EXHIBIT C

REDACTED

UNITED STATES DISTRICT COURT
DISTRICT COURT OF NEW JERSEY

IN RE: VALSARTAN PRODUCTS LIABILITY LITIGATION	Case No. 1:19-MD-2875-rbk

Expert Rebuttal Report of Dr. David Chan, MD, PhD

January 12, 2022

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I. INTRODUCTION

A. Qualifications

1. My name is David Chan. I am an Associate Professor of Health Policy (with Tenure) at Stanford University, a Faculty Fellow at the Stanford Institute for Economic Policy, an Investigator at the Center for Health Care Evaluation at the Department of Veterans Affairs, and a Faculty Research Fellow at the National Bureau of Economic Research.

2. I practice internal medicine as a Staff Physician at the Veterans Affairs Palo Alto Health Care System. Prior to my current positions, from 2010-2013 I was an Instructor of Medicine at Harvard Medical School. I received my MD from the University of California at Los Angeles in 2005. From 2005-2008, I completed my residency in internal medicine at Brigham and Women's Hospital, a teaching hospital of Harvard Medical School.

3. I received a PhD in Economics from the Massachusetts Institute of Technology, an MSc in Economics for Development at the University of Oxford, an MSc in International Health Policy at the London School of Economics, and a BA in Mathematics and Economics from the University of California at Riverside.

4. My research focuses on analyzing physician diagnosis and treatment decisions, variation in physician practices and skills, the use and appropriateness of clinical practice guidelines, and the effects of health policies and systems of care. This research has received funding by the National Institutes of Health, the Department of Veterans Affairs, and the Agency for Health Care Research and Quality. I have published my work in peer-reviewed journals of economics, health policy, and medicine, including *American Economic Journal: Economic Policy*, *Econometrica*, *Health Affairs*, *Health Services Research*, the *Journal of Political Economy*, the *New England Journal of Medicine*, and the *Quarterly Journal of Economics*, among others. I routinely serve as a peer-review referee for journals such as the *American Economic Review*, *Journal of the American Medical Association*, *Journal of Health Economics*, and *PLOS ONE*. I currently teach at Stanford on topics including Health Economics and Outcomes Analyses, and I have presented in academic and policy settings on numerous healthcare-related topics.

5. My CV, including a list of my publications, is attached as **Appendix A**, and a list of my testimony in the last four years is contained in **Appendix B**.

6. This report summarizes the opinions I have formed to date. I may update, refine, or revise my opinions, if necessary, based on further review and analysis of information provided to me subsequent to the filing of this report, or at the instruction of counsel or the Court. In addition, I reserve the right to prepare additional supporting materials, such as summaries, graphical exhibits, and charts.

B. Allegations

7. I have reviewed in its entirety the Consolidated Third Amended Medical Monitoring Class Action Complaint ("Medical Monitoring Complaint") and the Third Amended Consolidation Economic Loss Class Action Complaint ("Economic Loss Complaint") both dated November 1, 2021. I understand that, among other allegations, Plaintiffs allege that the Defendants marketed and sold "valsartan-containing drugs ('VCDs') that were contaminated with unintended nitrosamine impurities" including NDMA (N-nitrosodimethylamine) and NDEA (N-nitrosodiethylamine).[1] They further allege that "[a]ccording to the testing performed by the Defendants and the FDA, Defendants' generic VCDs contained NDMA and/or NDEA contamination levels that were unacceptable under all applicable standards."[2]

8. In regards to the proposed medical monitoring class, I further understand that, among the remedies requested, Plaintiffs "seek injunctive and monetary relief, including creation of a fund to finance independent medical monitoring services, including but not limited to notification to all people exposed to this contamination, examinations, testing, preventative screening, and care and treatment of cancer resulting, at least in part, from the exposure to the NDMA or NDEA contamination."[3] The proposed medical monitoring class consists of

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[1] Consolidated Third Amended Medical Monitoring Class Action Complaint, *Valsartan Products Liability Litigation*, November 1, 2021 (hereafter, "Medical Monitoring Complaint"), ¶2. *See also,* Third Amended Consolidated Economic Loss Class Action Complaint, *Valsartan, Losartan, and Irbesartan Products Liability Litigation*, November 1, 2021 (hereafter, "Economic Loss Complaint"), ¶2.

[2] Medical Monitoring Complaint, ¶5. *See also,* Economic Loss Complaint, ¶5.

[3] Medical Monitoring Complaint, ¶1.

individuals "who consumed a sufficiently high Lifetime Cumulative Threshold of NDMA, NDEA, or other nitrosamine, in generic valsartan-containing drugs manufactured by or for Defendants" starting in January 2012.[4] The Plaintiffs allege that these individuals "suffered cellular damage, genetic harm, and/or are at an increased risk of developing cancer as a result, but have not yet been diagnosed with cancer."[5]

9. Additionally, in regard to the proposed economic loss class, I understand that Plaintiffs allege that "the VCDs they purchased were so inherently flawed, unfit, or unmerchantable as to have no market value"[6] or "to have significantly diminished or no intrinsic market value."[7] The proposed economic loss class includes consumer and third-party payer ("TPP") subclasses. These proposed subclasses specifically include:

- "All consumers in the United States and its territories and possessions who, since at least January 1, 2012 to the present, paid any amount of money for a valsartan-containing drug (intended for personal or household use) that was manufactured, distributed, or sold by any Defendant.
- All TPPs in the United States and its territories and possessions that, since at least January 1, 2012 to the present, paid any amount of money for a valsartan-containing drug (intended for personal or household use) that was manufactured, distributed, or sold by any Active Pharmaceutical Ingredient, Finished Dose, Wholesaler, or Repackager/Relabeler Defendant."[8]

C. Assignment

10. For the proposed medical monitoring class, I have been asked by counsel for the Defendants to review the expert report submitted by Professor Zirui Song and to address certain opinions

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4 Medical Monitoring Complaint, ¶¶538-39.

5 Medical Monitoring Complaint, ¶1.

6 Economic Loss Complaint, ¶632.

7 Economic Loss Complaint, ¶¶651, 669, 687.

8 Economic Loss Complaint, ¶604.

offered by him.[9] As part of this assignment, I was asked to evaluate whether Professor Song established a common methodology for determining the health care spending that would accrue from the medical monitoring for proposed class members, and whether such a class-wide methodology was feasible and reliable. I was also asked to review the expert report submitted by Dr. Edward Kaplan and to comment on his proposal for screenings for the proposed medical monitoring class, particularly as it relates to Professor Song's methodology.[10]

11. Additionally, I was asked to review the expert report submitted by Dr. Rena Conti for the proposed economic loss class, and to comment on her economic framework used to assert that the valsartan products that were recalled due to possible nitrosamine impurity ("affected valsartan") are "worthless."[11]

12. This report and the opinions expressed in it are based on my analysis of the information and materials available to me as of this date as well as my training and experience. I hold the opinions that rely on my medical training and clinical experience to a reasonable degree of medical certainty. Likewise, I hold the opinions that rely on my experience and training in economics to a reasonable degree of certainty. I reserve the right to supplement this report if new information relevant to my opinions becomes available. A list of the materials that I have reviewed and relied upon in forming the opinions set forth in this report is included in **Appendix C**.

13. Professional staff at Analysis Group, Inc., under my direction, assisted me in preparing this report. I am being compensated for my work in this case at the rate of $850 per hour. In addition, I receive a portion of the fees paid to Analysis Group, Inc. for this work. This compensation is not contingent on the nature of my findings and opinions or on the outcome

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[9] Expert Report of Zirui Song, M.D., Ph.D., *Valsartan Products Liability Litigation,* November 10, 2021 (hereafter, "Song Report").

[10] Expert Report of Edward H. Kaplan, M.D., *Valsartan, Losartan, and Irbesartan Products Liability Litigation,* November 10, 2021 (hereafter, "Kaplan Report").

[11] Expert Declaration of Rena Conti, Ph.D., *Valsartan, Losartan, and Irbesartan Products Liability Litigation,* November 10, 2021 (hereafter, "Conti Report").

of this litigation. I understand that the Defendants in the above-referenced litigation may rely upon my expert testimony at trial.

II. SUMMARY OF CONCLUSIONS

A. Proposed Medical Monitoring Class Summary of Conclusions

14. Valsartan is prescribed to treat high blood pressure, heart failure, and left ventricular failure after a heart attack. Certain valsartan products have been identified as containing NDMA and NDEA, which have been found to be potential human carcinogens. The FDA has defined a certain amount of exposure to NDMA and NDEA as acceptable, based on a sufficiently small incremental risk of cancer. However, the FDA has determined that some valsartan products contained levels of NDMA and NDEA that may result in a greater, though still small, incremental increase in risk of cancer.[12] Plaintiffs have offered a class-wide medical monitoring program for their proposed medical monitoring class and claim a common methodology exists to determine healthcare spending for such a monitoring program.

15. In my opinion, a single medical monitoring program for an entire population of individuals as proposed by Plaintiffs and outlined by Dr. Kaplan and Professor Song is not clinically appropriate and is potentially harmful. Healthcare providers make decisions about the relevance and appropriateness of various cancer screening approaches based on individual patient factors, medical guidelines, and their assessment of the benefit-risk tradeoffs of conducting a given screening. Further, a common methodology to determine healthcare spending for such a monitoring program would not be feasible due the wide variability in

[12] Throughout this report, I use the term "affected valsartan" to refer to valsartan or any combination valsartan drug that was recalled due to possible nitrosamine impurity as identified on the FDA's website. *U.S. Food & Drug Administration,* "Search List of Recalled Angiotensin II Receptor Blockers (ARBs) including Valsartan, Losartan and Irbesartan," available at https://www.fda.gov/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and (hereafter, "FDA's Recalled NDC List"). *See also*, *U.S. Food & Drug Administration*, "Recalls of Angiotensin II Receptor Blockers (ARBs) including Valsartan, Losartan and Irbesartan," available at https://www.fda.gov/drugs/drug-safety-and-availability/recalls-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and-irbesartan.

services and costs and uncertainty in estimating the necessary services and costs for an unspecified time in the future.

16. ***Medical guidelines do not support extensive screening of asymptomatic patients in this case.*** In general, medical guidelines do not recommend screening broad groups of asymptomatic patients due to a single exposure factor that is not strongly linked to a particular type of cancer. Only for two of the nine cancers that Plaintiffs identify for screening in this case, colorectal and lung, do the guidelines recommend screening for a specific population based on either age or age and smoking history. While there are many risk factors for the nine types of cancers identified by Plaintiffs in this case, a high threshold must be met for a risk factor to be incorporated into a guideline to screen populations of asymptomatic patients. In my opinion, the evidence related to NDMA and NDEA in affected valsartan fails to meet the bar required to use a uniform screening process on a broad population of asymptomatic patients.

17. ***Cancer screening is not riskless, which is why clinical guidelines default to not recommending screenings for broad populations of patients.*** Overdiagnosis and false positives can result in increased and unnecessary follow-up testing and procedures that may carry their own risks, while negative screening results may result in false reassurance and may dissuade patients from self-monitoring signs and symptoms. Screening broad populations of patients for an array of cancers may lessen the accuracy of screening for patients with higher cancer risks. Additionally, specific screening procedures, like colonoscopies, have serious risks such as bleeding and perforation. The default recommendation from the guidelines not to screen reflects the fact that the risks of screening inherently outweigh the benefits on average in broad populations. In the case of most other cancer risks and clinical presentations, individual assessment is required to determine if the benefits would exceed the risks, and if so, recommendation for a screening would be given based on patient-specific, cancer-specific, procedure-specific reasons.

18. ***In assuming a single set of procedures as appropriate monitoring for nine different cancers in a broad set of patients, Professor Song's analysis fails to address the individualized nature of cancer screening decisions by healthcare providers and patients.*** Healthcare providers recommend cancer screenings that are relevant for a given patient based on their unique circumstances, including patient and family histories, lifestyle, age, preferences for treatment,

and many other factors, most of which have a much greater impact on the decision to screen than affected valsartan use or even carcinogen exposure.

19. To the extent carcinogen exposure is deemed a relevant consideration by a healthcare provider, individual patient exposure to carcinogens other than NDMA and NDEA, of which the U.S. Department of Health and Human Services has identified over 250, will vary based on a wide range of environmental factors. Even if a substance or exposure is known or suspected to cause cancer, the benefits patients receive from the substance or exposure can outweigh the risks. For example, while gamma and X-radiation are known to increase cancer risk by a small amount, the benefits of x-ray imaging exams, such as CT scans, as a valuable medical tool outweigh the risk. To the extent that nitrosamine exposure is deemed a relevant consideration by a particular healthcare provider, it is highly unlikely that judgment would be driven by a patient's affected valsartan use alone, but rather by exposure to NDMA and NDEA through other dietary, environmental, or endogenous sources, together with exposure to other potentially carcinogenic agents.

20. Depending on patient-specific risk factors, some proposed class members may be at low risk and never require cancer screening as a result of their use of affected valsartan, while others may be contraindicated for certain screening procedures. Other proposed class members may receive widely varying screening procedures dependent on their specific risk profile or symptoms, and still other proposed class members may receive cancer screening driven by better-established factors addressed by clinically supported medical guidelines and wholly unrelated to their use of affected valsartan.

21. ***Variation across patients in the appropriate screening procedures and the cost of those procedures make an aggregate calculation of total healthcare spending for the proposed medical monitoring class infeasible and unreliable.*** Beyond the issues of a single multi-cancer class-wide monitoring program assumed within Professor Song's "common methodology," his estimation of healthcare spending for such a program is fundamentally flawed. Despite acknowledgement from Professor Song that costs would vary based on insurance coverage, service location, and provider network status, his estimation fails to consider this variability in services and costs in the proposed medical monitoring class.

- First, variation in prices is well documented in many studies across and within payer types. My analysis of prices for Professor Song's set of six proposed procedures in various data sources including Massachusetts General Hospital ("MGH") outpatient pricing, the OptumHealth commercial insurance pricing, and Medicare charged amounts additionally demonstrate the high variability of prices for the selected procedures. Even for the same Current Procedural Terminology ("CPT") or Healthcare Common Procedure Coding System ("HCPCS") code associated with a procedure, the average price paid by patients in the proposed medical monitoring class may differ substantially from the national average prices presented in Dr. Song's analysis. Determining the appropriate price for any given procedure for the proposed class members would require individualized inquiry.

- Second, the spending associated with the medical procedures identified by Professor Song may not be accurately represented by the average spending by the CPT codes Professor Song includes in his report, which are not specific to the proposed class members. There are many different CPT or HCPCS codes associated with similar procedures, and different reasons why a screening procedure might be coded under a different CPT code for different patients, and therefore would incur different spending associated with that procedure. Determining the appropriate total cost of screening for the proposed class would require an individualized evaluation of the potential screening procedures that would be adopted for each patient and the associated costs to that patient.

- Third, Professor Song's analysis focuses on total service prices and does not account for patient cost-sharing, which can vary across patients and within patients across covered benefits, the provider the patient selects (i.e., in network or out of network), and other plan provisions. Based on the Plaintiffs' proposed class definition, I understand that patients are the relevant members of the proposed class, and the share of costs paid by proposed class members requires individualized analysis of patient cost-sharing.

- Lastly, the variation in prices, medical services, and cost-sharing mentioned above, which have seen substantial changes in the past, could change entirely in the future and

over the course of any proposed medical monitoring timeframe. Coverage of different medical services by various insurers could also shift especially with continued advancement in medical technology, which could change the medical guidelines and render some procedures obsolete with the potential introduction of simpler, less invasive, or less costly tests.

22. ***Taken together, Professor Song's approach does not provide a methodology to estimate aggregate healthcare spending for the proposed medical monitoring program.*** His methodology fails to consider and reliably incorporate the variability in prices, services, and patient cost-sharing. The various sources of variability I highlight demonstrate the need for individualized inquiry in determining whether a screening is appropriate for a patient and what that screening would cost at a given point of time. The difficulty of accounting for this variability is compounded by the fact that no one data source nor set of data sources provides all of this information for a consistent or comprehensive sample of patients.

B. Dr. Conti's "Worthless" Claim Summary of Conclusions

23. ***Dr. Conti does not consider, and provides no evaluation of, the value patients received from affected valsartan.*** Dr. Conti's claim that affected valsartan was "worthless" for all patients in the proposed economic loss class is premised on a hypothetical where patients would not have received affected valsartan and where she claims that there would be no equilibrium price nor value of a product without legitimate supply. This framework fails to evaluate the value of affected valsartan to those patients who *in fact received* the product. It is clear that affected valsartan was not "worthless" to all patients who received it—from either a medical or economic perspective—as Dr. Conti claims. Many of the patients who were treated with affected valsartan received its therapeutic benefit for treating their hypertension and/or heart failure.

24. From a medical perspective, this therapeutic benefit is certainly not "worthless," and even the FDA's own assessment indicates an extremely low (and variable) potential risk of cancer associated with affected valsartan. The FDA also recognizes that the benefits of affected valsartan generally outweigh the risks. For example, the FDA noted that "the risks of stopping taking [sic] an ARB product for treating high blood pressure and heart failure greatly

outweighs [sic] the potential risk of exposure to trace amounts of nitrosamines."[13] Thus, most patients received the benefits of valsartan with little to no increased risk of cancer. The value received by patients from taking affected valsartan varies across patients given their individual situation, including their individual medical history, lifestyle, and underlying conditions.

25. From an economic perspective, all of these considerations will factor into a willingness to pay for valsartan. The fact that patients have already taken affected valsartan means that one should consider this object of willingness to pay rather than the "equilibrium" price in a hypothetical scenario in which the affected valsartan products ceased to exist. The equilibrium price represents a lower bound on willingness to pay across all consumers who choose to purchase a product and therefore cannot be used to judge value for each patient in any scenario. In addition to the medical considerations, willingness to pay will also depend on the state of information about NDMA and NDEA in affected valsartan, which varied at different points in the timeline for all parties involved; on alternative treatments that depend on patients, providers, and third-party payers; and on risk preferences of patients. Dr. Conti simply ignores these factors.

III. VALSARTAN AND EXPOSURE TO NITROSAMINES

A. Valsartan

26. Valsartan is an angiotensin II receptor blocker ("ARB") used to treat high blood pressure, heart failure, and left ventricular failure after a heart attack.[14] Other ARBs include losartan and irbesartan. Valsartan was first approved by the U.S. Food & Drug Administration ("FDA") in 1996 under the trade name Diovan®.[15] A combination pill containing valsartan and amlodipine

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[13] *U.S. Food & Drug Administration*, "Statement of the Agency's Ongoing Efforts to Resolve Safety Issue with ARB Medications," August 28, 2019, available at: https://www.fda.gov/news-events/press-announcements/statement-agencys-ongoing-efforts-resolve-safety-issue-arb-medications.

[14] *Mayo Clinic*, "Valsartan (Oral Route)," July 1, 2021, available at https://www.mayoclinic.org/drugs-supplements/valsartan-oral-route/proper-use/drg-20067355.

[15] *U.S. Food & Drug Administration,* "Drugs@FDA: FDA-Approved Drugs," available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020665.

was later approved under the trade name Exforge® in 2007.[16] Generic versions of both Diovan® and Exforge® have since entered the US market, with multiple abbreviated new drug applications now approved for each drug.[17,18] Defendants in this matter are manufacturers, distributors, and retail pharmacies involved in the manufacture, distribution, or sale of generic versions of Diovan® and Exforge®.[19]

B. NDMA and NDEA

27. N-nitrosamines (also known as "nitrosamines") are organic compounds formed by chemical reactions between nitrites and certain amines.[20] While nitrosamines have no inherent industrial use, they are commonly found in consumer products due to the nature of the products' manufacturing, preparation, and/or processing.[21] Many nitrosamines are described by the U.S. National Toxicology Program as "reasonably anticipated to be a human carcinogen" based on

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16 *U.S. Food & Drug Administration,* "Drugs@FDA: FDA-Approved Drugs," available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021990.

17 *U.S. Food & Drug Administration,* "Drugs@FDA: FDA-Approved Drugs," available at https://www.accessdata.fda.gov/scripts/cder/daf/ (search for "valsartan").

18 "Valsartan and Valsartan Containing Drugs (hereafter "VCDs") are the generic versions of the reference listed drugs ("RLDs") DIOVAN® and/or EXFORGE®, which were the brand names." *See* Memorandum of Law in Support of the Medical Monitoring Plaintiffs' Motion for Class Certification, *Valsartan, Losartan, and Irbesartan Products Liability Litigation,* November 10, 2021 (hereafter, "Memorandum of Law") at FN 1.

19 Memorandum of Law, p. 1.

20 *See, e.g., World Health Organization,* "Information Note Nitrosamine impurities," November 20, 2019, available at https://www.who.int/news/item/20-11-2019-information-note-nitrosamine-impurities. *See also*, Beard, Jessica C., and Timothy M. Swager, "An Organic Chemist's Guide to N-Nitrosamines: Their Structure, Reactivity, and Role as Contaminants," *The Journal of Organic Chemistry, Vol.* 86, No. 3 January 21, 2021, pp 2037–2057.

21 *National Toxicology Program, Department of Health and Human Services*, "N-Nitrosamines: 15 Listings," December 21, 2021, available at https://ntp.niehs.nih.gov/ntp/roc/content/profiles//nitrosamines.pdf.

evidence of carcinogenicity in animal studies.[22] NDMA and NDEA are two such nitrosamines identified as impurities in the affected valsartan products.[23]

28. The FDA has defined acceptable intake levels of NDMA and NDEA to be 0.096 µg/day and 0.0265 µg/day, respectively, which are daily exposures that would approximate a 1 in 100,000 cancer risk after 70 years of exposure.[24] A 1 in 100,000 cancer risk is considered "acceptable" for marketed pharmaceutical products given how small it is relative to the overall risk humans face for developing cancer (over 1 in 3).[25] However, other sources estimate that even higher levels of exposure to NDMA and NDEA may be acceptable according to these standards.[26]

29. The FDA has used these acceptable intake levels described above to estimate a small incremental risk of cancer associated with valsartan use but has not determined a risk specific to any particular type of cancer. Based on a laboratory analysis of the levels of impurities detected in recalled batches of affected valsartan, the FDA estimated that 1 in 8,000 people who took the *highest* valsartan dose (320 mg) with NDMA daily for four years may develop cancer in their 70-year lifetime and that 1 in 18,000 people who took the *highest* valsartan dose

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[22] *National Toxicology Program, Department of Health and Human Services*, "N-Nitrosamines: 15 Listings," December 21, 2021, available at https://ntp.niehs.nih.gov/ntp/roc/content/profiles//nitrosamines.pdf.

[23] Throughout this report, I use the term "affected valsartan" to refer to valsartan or any combination valsartan drug that was recalled due to possible nitrosamine impurity. Valsartan and combination valsartan drugs subject to recall are identified by the FDA by National Drug Code ("NDC") and manufacturing lot number. For my analyses in this report, I used the list of NDCs identified as recalled on the FDA's website to determine 'affected valsartan' products (as manufacturing lot numbers are not available in the data I use for analysis). *See* FDA's Recalled NDC List. *See also*, *U.S. Food & Drug Administration*, "Recalls of Angiotensin II Receptor Blockers (ARBs) including Valsartan, Losartan and Irbesartan," available at https://www.fda.gov/drugs/drug-safety-and-availability/recalls-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and-irbesartan.

[24] *U.S. Food & Drug Administration*, "FDA Updates and Press Announcements on Angiotensin II Receptor Blocker (ARB) Recalls (Valsartan, Losartan, and Irbesartan)," November 7, 2019, available at https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan.

[25] *U.S. Food & Drug Administration,* "M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk: Guidance for Industry," March 2018, available at https://www.fda.gov/media/85885/download.

[26] Johnson, George E., *et al.,* "Permitted Daily Exposure Limits for Noteworthy N-nitrosamines," *Environmental and Molecular Mutagenesis*, Vol. 62, No. 5, May 11, 2021, pp. 293–305.

(320 mg) with NDEA daily for four years may develop cancer in their 70-year lifetime.[27] Since these estimates are based on the highest daily dose and many people take much lower doses, the FDA expects that the actual cancer risk to most patients taking affected valsartan would be lower than these estimates.[28] The FDA's estimates also assume continuous exposure to affected valsartan for four years given that "the impurities may have been present in valsartan-containing finished drug lots for up to four years."[29] The actual duration of at-risk exposure may be much lower for many patients due to variability in therapy duration and variability in impurity levels across affected valsartan products (described further in **Section V.C**). The possibility that the FDA's estimates overstate incremental cancer risk for many patients is consistent with evidence from two European studies, both of which found that exposure to affected valsartan was not associated with a significantly elevated risk of developing cancer overall.[30,31]

30. Nitrosamine-containing valsartan is not the sole, or even a primary, source of NDMA or NDEA exposure. Humans are routinely exposed to nitrosamines, including NDMA and NDEA, through numerous everyday exogenous and endogenous sources other than affected valsartan.

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[27] *U.S. Food & Drug Administration*, "Laboratory analysis of valsartan products," May 2, 2019, available at https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products. *U.S. Food & Drug Administration*, "FDA Updates and Press Announcements on Angiotensin II Receptor Blocker (ARB) Recalls (Valsartan, Losartan, and Irbesartan): FDA updates table of interim limits for nitrosamine impurities in ARBs," February 28,2019, available at https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan#interimlimits2.

[28] *U.S. Food & Drug Administration*, "Laboratory analysis of valsartan products," May 2, 2019, available at https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products.

[29] *U.S. Food & Drug Administration*, "Laboratory analysis of valsartan products," May 2, 2019, available at https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products.

[30] Pottegård, Anton, *et al.*, "Use of N-Nitrosodimethylamine (NDMA) Contaminated Valsartan Products and Risk of Cancer: Danish Nationwide Cohort Study," *BMJ,* Vol. 362, September 12, 2018, pp. 1–7. *See also*, Gomm, Willy, *et al*., "N-Nitrosodimethylamine-Contaminated Valsartan and the Risk of Cancer: A Longitudinal Cohort Study Based on German Health Insurance Data," *Deutsches Ärzteblatt International*, Vol. 118, No. 21, May 28, 2021, pp. 357–362, at 357.

[31] While neither study found a significant relationship between exposure to contaminated valsartan and *overall* cancer risk, the German study found exposure to affected valsartan to be associated with a significantly elevated risk of hepatic cancer. Gomm, Willy, *et al*., "N-Nitrosodimethylamine-Contaminated Valsartan and the Risk of Cancer: A Longitudinal Cohort Study Based on German Health Insurance Data," *Deutsches Ärzteblatt International*, Vol. 118, No. 21, May 28, 2021, pp. 357–362.

Dietary sources of NDMA exposure, for example, are acknowledged by Plaintiffs' expert Dr. Dipak Panigrahy:

> NDMA can also be found in many processed foods and beverages such as beer, cured meats, bacon, smoked and salted fish, and cheeses … NDMA is also an unintended byproduct of the chlorination of wastewater and drinking water at treatment plants that use chloramines for disinfection.[32]

Dietary sources of nitrosamines are not limited to these examples. In fact, levels of NDMA and/or NDEA have been detected in over 70 different foods and beverages.[33] Humans may also be exposed to NDMA through environmental and occupational sources. NDMA can be found in personal care products (e.g., shampoos, detergents, cosmetics), rubber-containing products (e.g., latex disposable gloves, pacifiers), and tobacco products.[34] Many workplaces also pose an exposure risk to NDMA, particularly those associated with the manufacturing and/or processing of the above-mentioned products.[35] Humans also generate nitrosamines endogenously through internal processes, at levels that have been estimated to far exceed all exogenous sources of nitrosamine exposure combined.[36]

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[32] Rule 26 Expert Report of Dipak Panigrahy, M.D., *Valsartan, Losartan, and Irbesartan Products Liability Litigation*. July 6, 2021 (hereafter, "Panigrahy Report"), at p. 32.

[33] Park, Jong-eun, *et al.,* "Distribution of Seven N-Nitrosamines in Food," *Toxicological Research,* Vol. 31, No. 3, September 30, 2015, pp. 279–288.

[34] *World Health Organization*, "Concise International Chemical Assessment Document 38, N-Nitrosodimethylamine," 2002, available at https://www.who.int/ipcs/publications/cicad/en/cicad38.pdf.

[35] *World Health Organization*, "Concise International Chemical Assessment Document 38, N-Nitrosodimethylamine," 2002, available at https://www.who.int/ipcs/publications/cicad/en/cicad38.pdf.

[36] Fristachi, Anthony, and Glenn Rice, "Estimation of the Total Daily Oral Intake of NDMA Attributable to Drinking Water," *Journal of Water and Health*, Vol. 5, No. 3, 2007, pp. 341–355 (Estimate that endogenous formation is responsible for 99% of daily NDMA intake). *See also*, Tricker, A.R., "N-Nitroso Compounds and Man: Sources of Exposure, Endogenous Formation and Occurrence in Body Fluids." *European Journal of Cancer Prevention*, Vol. 6, No. 3, 1997, pp. 226–268 (Analyses suggest that endogenous formation is responsible for between 45% and 75% of total human exposure to nitrosamines).

IV. IMPORTANT CLINICAL CONSIDERATIONS OF MEDICAL GUIDELINES ON CANCER SCREENINGS

31. Professor Song's analysis fails to consider the individualized patient considerations that shape cancer screening practices and the clinical ramifications of the proposed medical monitoring program.[37] As I discuss in further detail below, cancer screenings need to be tailored to each individual patient, given a variety of factors. When cancer screenings are recommended for patients, healthcare providers make decisions about the relevance and appropriateness of various cancer screening approaches based on individual patient factors, medical guidelines, and their assessment of the benefit-risk tradeoffs of conducting a given screening. Including a broad group of patients for cancer screening may entail risks to these patients and externalities to the patients who are already being screened. Therefore, cancer screening should not readily be performed even when new (potentially small) cancer risks are discovered unless sufficient clinical evidence has shown that the benefits outweigh the risks and externalities in a broad, asymptomatic population or a healthcare provider as deemed it beneficial for a specific patient based on individual circumstances.

32. Once patients have symptoms, healthcare providers will make decisions about what diagnostic testing is appropriate to check for cancer and, if applicable, intervene during the early stages of cancer. This diagnostic testing is targeted and weighs different benefits and risks because the patient is symptomatic. In contrast, the screening guidelines I discuss in this section refer to the testing of an apparently healthy, asymptomatic target population.[38] Such guidelines are applicable to the proposed medical monitoring class, as there is no requirement that members of the proposed class experience any symptoms of cancer resulting from the affected valsartan. According to the American Cancer Society, common signs and symptoms of cancer include fatigue, weight loss, changes in bowel habits, headaches, and vision problems.[39] In general, an

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[37] Cancer screenings refer to tests and procedures for asymptomatic patients.

[38] *National Cancer Institute*, "Cancer Screening Overview (PDQ®)–Patient Version," August 19, 2020, available at https://www.cancer.gov/about-cancer/screening/patient-screening-overview-pdq.

[39] *American Cancer Society*, "Signs and Symptoms of Cancer," November 6, 2020, available at https://www.cancer.org/treatment/understanding-your-diagnosis/signs-and-symptoms-of-cancer.html.

estimated 50% of patients with cancer present with "nonspecific or vague symptoms" not associated with a specific cancer.[40] Further, those symptoms which are associated with cancer are not necessarily specific to one form of cancer; for example, abdominal pain is a common symptom of colorectal, ovarian, and renal cancer.[41] Because of the vague nature of early cancer symptoms, individuals experiencing symptoms are advised to speak to their healthcare providers who can then provide individualized testing and care based on multiple symptoms, comorbidities, and other relevant information.[42]

33. Since early cancer symptoms can overlap with symptoms for many other medical issues, proposed class members may already receive the tests in the proposed monitoring program in response to symptoms unrelated to cancer, as discussed further in **Section V.A.1**. For example, patients experiencing symptoms of irritable bowel syndrome may receive stool tests, upper endoscopy, or colonoscopy.[43] Individuals with a chronic cough may be given a chest X-ray to check for infection or cancer.[44] Lab tests such as urinalysis may be provided to patients experiencing symptoms of a urinary tract infection.[45]

34. In this section, I outline the widely accepted medical screening guidelines for asymptomatic patients related to the cancers specified by Plaintiffs in this matter and discuss the benefits and risks associated with cancer screening procedures. This context is important to understand the individualized nature of patient care as well as how clinical care decisions are made and would be made for patients exposed to affected valsartan. Recommendations to screen *populations* of

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[40] Koo, Minjoung, *et al.*, "Conceptual Framework to Guide Early Diagnosis Programs for Symptomatic Cancer as Part of Global Cancer Control," *JCO Global Oncology,* Vol. 7, 2021, pp. 35–45, at p. 38.

[41] Koo, Minjoung, *et. al.*, "Symptom Signatures and Diagnostic Timeliness in Cancer Patients: A Review of Current Evidence," *Neoplasia,* Vol. 20, No. 2, February 2018, pp. 165–174.

[42] Scheel, Benedicte Iversen, *et. al.*, "Cancer suspicion in general practice: the role of symptoms and patient characteristics, and their association with subsequent cancer," *British Journal of General Practice*, Vol. 63, No. 614, 2013, pp. e627–e635, at p. e628.

[43] Mayo Clinic, "Irritable bowel syndrome," December 1, 2021, available at https://www.mayoclinic.org/diseases-conditions/irritable-bowel-syndrome/diagnosis-treatment/drc-20360064.

[44] Mayo Clinic, "Chronic cough," July 9, 2019, available at https://www.mayoclinic.org/diseases-conditions/chronic-cough/diagnosis-treatment/drc-20351580.

[45] Mayo Clinic, "Urinalysis," October 14, 2021, available at https https://www.mayoclinic.org/tests-procedures/urinalysis/about/pac-20384907.

asymptomatic patients who meet certain criteria are taken very seriously by medical societies and expert panels. In my opinion, the evidence related to NDMA and NDEA in affected valsartan fails to meet the bar required to uniformly screen a population of asymptomatic patients.

A. Medical guidelines on cancer screenings

1. Screening recommendations for asymptomatic patients

35. **Figure 1** outlines the recommendation status for screenings of various cancer types defined by the US Preventative Services Task Force ("USPSTF"), a volunteer panel of national experts, and the evidence-based reviews provided by the National Cancer Institute ("NCI"), the U.S. federal government's principal agency for cancer research. The USPSTF issues formal screening recommendations described as the "gold standard" in clinical preventive services.[46] USPSTF recommendations are based on a framework which considers questions such as whether screening may reduce morbidity; whether sufficiently sensitive and specific screening tests are available; whether early detection and treatment makes a difference in morbidity; and what the potential harms of screening and subsequent screening-implied treatment may be.[47] As the USPSTF has not published recommendations for all cancers specified by Plaintiffs, I also cite the NCI's evidence-based reviews on cancer screening. The NCI publishes reports describing whether a standard screening approach exists; the balance of risks and benefits associated with screening; and the levels of evidence associated with specific screening.[48]

36. In general, screening guidelines do not recommend screening of all asymptomatic people for all types of cancers. Even in categories of people where the risk of cancer is sufficiently high and effective screening methods exist, the decision to screen may depend on a number of

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[46] American Academy of Family Physicians (AAFP), *et al.*, "Open Letter to HHS Secretary Kathleen Sebelius," *First Annual Report to Congress on High-Priority Evidence Gaps for Clinical Preventive Services - I,* December 2011, available at https://www.uspreventiveservicestaskforce.org/uspstf/first-annual-report-congress-high-priority-evidence-gaps-clinical-preventive-services-i.

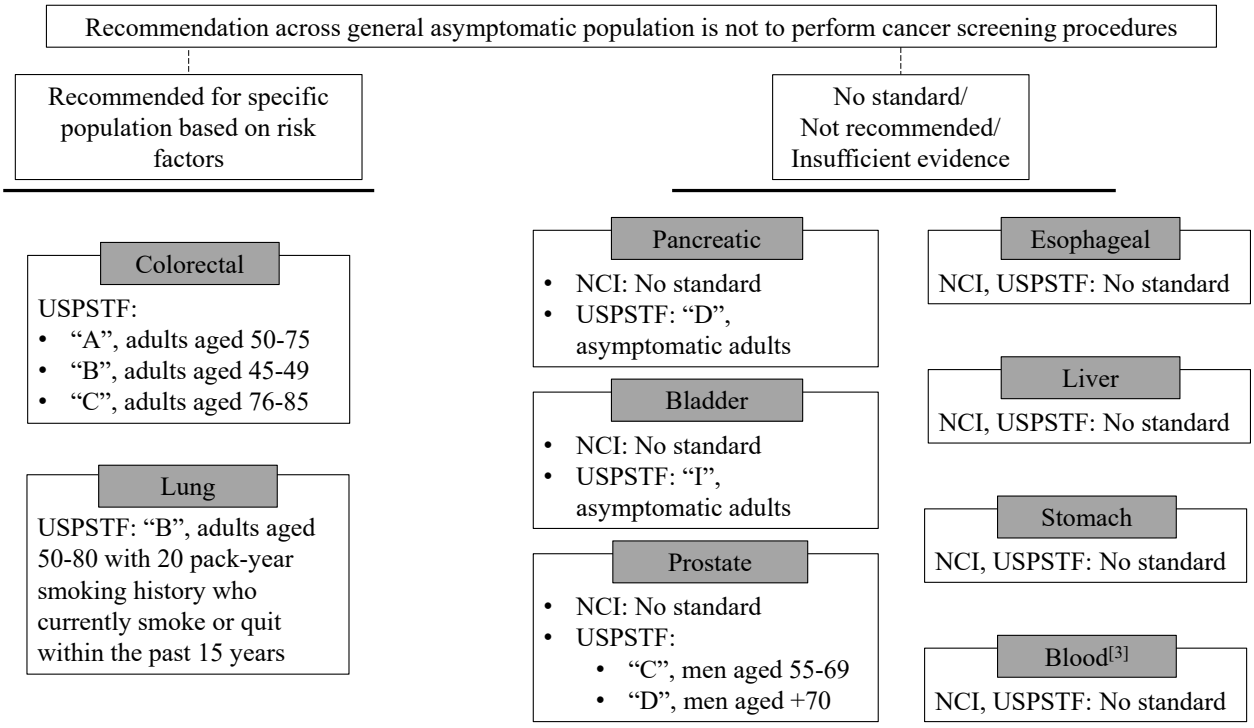
[47] Vearrier, David and Michael I. Greenberg, "The implementation of medical monitoring programs following potentially hazardous exposures: a medico-legal perspective," *Clinical Toxicology*, 2017, Vol. 55, No.9, June 23, 2017, pp. 956–969, at 959.

[48] *National Cancer Institute*, "Cancer Screening Overview (PDQ®)-Health Professional Version," June 2021, available at https://www.cancer.gov/about-cancer/screening/hp-screening-overview-pdq.

factors including patient history, comorbidities, and preferences. As summarized in **Figure 1**, only two of the nine cancers specified by Plaintiffs in this matter are recommended for screening of specific patient populations. The remaining seven of the nine cancers specified by Plaintiffs are associated with no standard screening recommendation or have screening explicitly discouraged due to the harms or a lack of sufficient benefit.[49] For all types of cancer, the USPSTF and NCI emphasize the individualized and personal nature of the decision given substantial tradeoffs between the potential benefits and harms associated with screening and subsequent screening-implied treatment.

[49] While other guidelines may exist, they can vary, which further emphasizes that the decision to screen a patient for cancer is individualized.

Figure 1. Selected screening guidelines [1],[2]



Notes:

[1] USPSTF grade recommendations provided; multiple grades reflect differing recommendations by sub-group. "A" and "B" imply screening is recommended, but with varying degrees of certainty regarding the net benefits. "C" denotes a recommendation for screening of selected patients based on individual circumstances. "D" reflects a recommendation against the service, given a moderate to high certainty that the benefits do not outweigh the harms of screening. "I" means that insufficient evidence exists to assess the net benefits.

[2] "No Standard" means no publication by the USPSTF or the NCI has stated that "no standard or routine test" exists. In the case of colorectal and lung cancers, the NCI has published reviews of screening consistent with USPSTF guidelines.

[3] Blood cancers referenced in figure are leukemia, myeloma, and lymphoma (Hodgkins and non-Hodgkins).

Sources:

[1] *U.S. Preventive Services Task Force*, "Published Recommendations," available at https://www.uspreventiveservicestaskforce.org/uspstf/topic_search_results?topic_status=P.

[2] *National Cancer Institute*, "PDQ® - Cancer Information Summaries: Screening/Detection (Testing for Cancer)," available at https://www.cancer.gov/publications/pdq/information-summaries/screening.

[3] *National Cancer Institute,* "Pancreatic Cancer - Patient Version," available at https://www.cancer.gov/types/pancreatic.

[4] *National Cancer Institute,* "Leukemia - Patient Version," available at https://www.cancer.gov/types/leukemia.

[5] *National Cancer Institute,* "Lymphoma - Patient Version," available at https://www.cancer.gov/types/lymphoma.

[6] *National Cancer Institute,* "Plasma Cell Neoplasms (Including Multiple Myeloma) - Patient Version," available at https://www.cancer.gov/types/myeloma.

37. Recommendations for screening of two of the nine cancers identified by Plaintiffs have been issued in cases where the benefits of screening of specific populations have been deemed sufficiently high: colorectal cancer and lung cancer. For both cancers, as described in **Figure 1**, the USPSTF recommends screening of individuals of a particular age range and behavioral history that can be ascertained by clinicians. In the case of colorectal cancer, the USPSTF recommends screening of adults 45-85 years of age. However, the USPSTF emphasizes less certainty regarding the benefits of screening those aged 45-49 and recommends only "selective" screening of those aged 76-85 based on each individual patient's health and preferences.[50] Similarly, for lung cancer screening, the USPSTF recommends screening of a specific population: an annual low-dose chest CT scan for adults aged 50 to 80 with a 20 pack-year history of smoking who have not quit within the past 15 years. But for other adults, particularly those with other health problems that limit their life expectancy or ability to endure curative lung surgery, annual screening is not recommended.[51]

38. In addition, the USPSTF does not recommend all screening technologies even for patients where some form of screening may be recommended. Lung cancer has a range of possible screening tests, but tests such as chest radiography and sputum cytology are not recommended due to their relatively low sensitivity and specificity in the detection of lung cancer.[52] The negative predictive value and positive predictive value will depend on the prevalence of the disease and on the operating characteristics of the screening technology.

39. For six of the nine cancers identified by Plaintiffs, the USPSTF or NCI (1) have not published screening guidelines; (2) have published screening guidelines but found that there is insufficient evidence to recommend the screening of asymptomatic individuals; or (3) have published screening guidelines but determined that there is insufficient evidence to recommend screening except on an individualized basis. Specifically, in the case of esophageal, liver,

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[50] U.S. Preventive Services Task Force, "Screening for Colorectal Cancer," *JAMA*, Vol. 325, No. 19, 2021, pp. 1965–1977, at p. 1968.

[51] *U.S. Preventive Services Task Force*, "Screening for Lung Cancer," *JAMA*, Vol. 325, No.10, March 9, 2021, pp. 962–970, at p. 963.

[52] Moyer, Virginia A., "Screening for Lung Cancer: U.S. Preventive Services Task Force Recommendation Statement," *Annals of Internal Medicine,* Vol. 160, No. 5, March 2014, pp. 330–338, at 332.

stomach, and blood cancers, there is no standard or routine screening guideline defined by the USPSTF or the NCI, for reasons including a lack of sufficient clinical evidence.[53] In the case of bladder cancer, for which the NCI has also stated that no standard screening exists, the USPSTF has issued an "insufficient evidence" decision for screening on the basis that more research is needed on the balance of harms and benefits with respect to screening of asymptomatic patients.[54] Finally, in the case of pancreatic cancer, the USPSTF issued a "do not screen" guideline to clinicians with respect to screening in asymptomatic adults, finding no evidence that screening improves disease-specific or all-cause mortality, and finding adequate evidence of moderate harm due to the risk of false-positives and the harms associated with treatment of true-positive, screen-detected pancreatic cancers due to "the poor prognosis for pancreatic cancer even when treated at an early stage."[55] Treatment of screen-detected pancreatic cancer could include procedures such as pancreatectomy, which carries a significant risk of mortality and morbidity.[56]

40. For the ninth cancer identified by Plaintiffs, prostate cancer, the USPSTF issued a "do not screen" guideline for men aged 70 or older, and specified for men aged 55 to 69 that the decision to undergo screening should be an individual one, made by the patient after discussion with a health care provider.[57] The USPSTF has noted that the "magnitude of the net benefit" of screening depends upon how each man "weighs the potential benefits and harms of

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[53] "More studies are needed to find out if it would be worthwhile to screen people in the United States who do have a high risk for stomach cancer." *National Cancer Institute,* "Stomach (Gastric) Cancer Screening (PDQ®)-Patient Version," available at https://www.cancer.gov/types/stomach/patient/stomach-screening-pdq.

[54] *National Cancer Institute,* "Bladder and Other Urothelial Cancers Screening (PDQ®)–Patient Version," available at https://www.cancer.gov/types/bladder/patient/bladder-screening-pdq;.Moyer, Virginia A., "Screening for Bladder Cancer: U.S. Preventive Services Task Force Recommendation Statement," *Annals of Internal Medicine,* Vol. 155, No. 4, August 2011, pp. 246–251, at 247.

[55] *U.S. Preventive Services Task Force*, "Screening for Pancreatic Cancer," *JAMA,* Vol. 322, No. 5, August 2019, pp. 438–444, at p. 440.

[56] *U.S. Preventive Services Task Force*, "Screening for Pancreatic Cancer," *JAMA,* Vol. 322, No. 5, August 2019, pp. 438–444, at p. 442.

[57] *U.S. Preventive Services Task Force*, "Screening for Prostate Cancer," *JAMA,* Vol. 319, No. 18, May 8, 2018, pp. 1901–1913, at p. 1901.

screening, diagnosis, and treatment," particularly in light of serious side effects such as erectile dysfunction and urinary incontinence.[58]

2. Individualized risk factors used to identify patients for screening

41. Within the guidelines for each of the cancers identified by Plaintiffs, the specific screening recommendations vary depending on the patient's age, medical history, and other individualized characteristics and situations. That is, the guidelines do not treat screening procedures as a single uniform approach applied to all patients, but instead emphasize the importance of a patient's medical history when considering the clinical relevance of a screening procedure. Additionally, as mentioned above, because screening is an individualized decision, the default recommendation for populations of asymptomatic patients, despite most specific risk factors, is not to screen.

42. **Figure 2** shows the risk factors used to define a specific population for asymptomatic screening for each cancer type considered by Plaintiffs. As these widely accepted medical screening guidelines demonstrate, a high threshold must be met for a risk factor to be incorporated into a guideline to screen populations of patients. While there are a multitude of risk factors for each type of cancer, only age and smoking history together with age are used to define the specific population recommended for colorectal and lung cancer screening, respectively. Notably, the age-adjusted relative risk ("RR") of lung cancer is 8.2 (95% confidence interval ("CI"): 4.6-14.5) for individuals with a 20 to 30 pack-year history of smoking, which is the pack-year threshold recommended by the USPSTF to determine eligibility for screening.[59] Regular smokers with a less than 20 pack-year history also have an elevated lung cancer risk, with a relative risk of 4.9 (95% CI: 2.6-9.3).[60] Other risks for lung cancer include having one first-degree family member affected (RR of 2.57, 95% CI: 2.39-2.76), or treatment with

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[58] *U.S. Preventive Services Task Force*, "Screening for Prostate Cancer," *JAMA,* Vol. 319, No. 18, May 8, 2018, pp. 1901–1913, at p. 1910.

[59] Yun, Young Ho, "Relative and Absolute Risks of Cigarette Smoking on Major Histologic Types of Lung Cancer in Korean Men," *Cancer Epidemiology, Biomarkers & Prevention*, Vol. 14, No. 9, September 2005, pp. 2125–2130, at p. 2128.

[60] Yun, Young Ho, "Relative and Absolute Risks of Cigarette Smoking on Major Histologic Types of Lung Cancer in Korean Men," *Cancer Epidemiology, Biomarkers & Prevention*, Vol. 14, No. 9, September 2005, pp. 2125–2130, at p. 2128.

radiation therapy (RR 2.04, 95% CI: 1.24-3.36).[61] With respect to colorectal cancer, risks include obesity (RR 1.54, 95% CI: 1.01-2.35), high alcohol consumption relative to non-drinkers (RR 1.71, 95% CI: 1.62-1.80), and a family history in a first-degree family member (RR 4.21, 95% CI: 2.61-6.79).[62] Even with these substantial relative risks, again, only age and smoking history are used to define the specific population recommended for colorectal and lung cancer screening.

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[61] Cannon-Albright, Lisa A., *et. al.*, "Population-Based Relative Risks for Lung Cancer Based on Complete Family History of Lung Cancer," *Journal of Thorasic Oncology*, Vol. 14, No. 7, July 1, 2019, pp. 1184–1191, at p. 184; Treatment by radiotherapy associated with lung cancer in smokers treated for breast cancer. Prochazka, Michaela, *et al.*, "Ionizing Radiation and Tobacco Use Increases the Risk of a Subsequent Lung Carcinoma in Women With Breast Cancer: Case-Only Design," *Journal of Clinical Oncology*, Vol. 23, No. 30, October 20, 2005, pp. 7467–7474.

[62] O'Sullivan DE, Sutherland RL, Town S, Chow K, Fan J, Forbes N, Heitman SJ, Hilsden RJ, Brenner DR, "Risk Factors for Early-Onset Colorectal Cancer: A Systematic Review and Meta-analysis," *Clin Gastroenterol Hepatol*, 2021, pp. 1–17, at p. 1.

Figure 2. Risk factors used to define population for screening

Cancer type	Risk factors	
	Used to define population for asymptomatic screening	**Not used to define population, but considered by physician in determining patient's individualized risk**
Colorectal	Age	Family history of colorectal cancer; personal history of previous colorectal cancer, high-risk adenomas, ovarian cancer or inflammatory bowel disease; inherited risk familial adenomatous polyposis (FAP) or hereditary nonpolyposis colon cancer (HNPCC or Lynch Syndrome); alcohol; cigarette smoking; Black race; and obesity.
Lung	Age and smoking history	Environmental exposures, prior radiation therapy, other (noncancer) lung diseases, and family history.
Pancreatic		New-onset diabetes, preexisting diabetes, older age, cigarette smoking, obesity, or a historyof chronic pancreatitis. Additionally, certain inherited genetic syndromes or a history of familial pancreatic cancer are high-risk factors.
Esophageal		Adenocarcinoma: Having gastroesophageal reflux disease (GERD), having Barrett esophagus, having a history of using drugs that relax the lower esophageal sphincter, being overweight. Squamous cell: Using tobacco, drinking a lot of alcohol, being malnourished (lacking nutrients and/or calories), being infected with human papillomavirus (HPV), having tylosis, having achalasia, having swallowed lye (a chemical found in some cleaning fluids), drinking very hot liquids on a regular basis.
Bladder		Smoking, occupational exposure to carcinogens (e.g., rubber, chemical, and leather industries), male sex, older age, White race, infections caused by certain bladder parasites, and family or personal history of bladder cancer.
Liver		Having hepatitis B and/or hepatitis C, having cirrhosis (potentially caused by hepatitis, especially hepatitis C, or drinking large amounts of alcohol for many years or being an alcoholic), and eating foods tainted with aflatoxin (poison from a fungus that can grow on foods, such as grains and nuts, that have not been stored properly).
Stomach		Having any of the following medical conditions: helicobacter pylori infection of the stomach, chronic gastric atrophy, pernicious anemia, intestinal metaplasia, polyps in the stomach, familial adenomatous polyposis (FAP), hereditary nonpolyposis colon cancer (HNPCC); having a mother, father, sister, or brother who has had stomach cancer; having had a partial gastrectomy; eating a diet high in salted, smoked foods or low in fruits and vegetables; eating foods that have not been prepared or stored the way they should be; and smoking cigarettes.
Blood		Leukemia: Exposure to cancer-causing agents, smoking, history of radiation therapy or chemotherapy, myelodysplastic syndromes, rare genetic syndromes, and family history. Multiple Myeloma: Male sex, Black race, family history, obesity, monoclonal gammopathy of undetermined significance (MGUS) or solitary plasmacytoma. Hodgkin Lymphoma: Epstein-Barr virus infection/mononucleosis, age, male sex, family history, weakened immune system. Non-Hodgkin Lymphoma: Older age, sex, White race, geography (more common in developed countries), family history, exposure to certain chemicals and drugs, radiation exposure, weakened immune system, autoimmune diseases, certain infections.
Prostate		Age, race, family history of prostate cancer, alcohol consumption, vitamin or mineral interactions, and other dietary habits.

Note: Figure describes risk factors used to define population for asymptomatic screening as per USPSTF recommendations. The USPSTF, the NCI, and other sources referenced to determine list of risk factors.

Sources:

[1] *U.S. Preventive Services Task Force*, "Published Recommendations," available at https://www.uspreventiveservicestaskforce.org/uspstf/topic_search_results?topic_status=P.

[2] *National Cancer Institute*, "PDQ® - Cancer Information Summaries: Screening/Detection (Testing for Cancer)," available at https://www.cancer.gov/publications/pdq/information-summaries/screening.

[3] *Memorial Sloan Kettering Cancer Center*, "Risk Factors for Leukemia," available at https://www.mskcc.org/cancer-care/types/leukemias/risk-factors; *American Cancer Society*, "Risk Factors for Multiple Myeloma," available at https://www.cancer.org/cancer/multiple-myeloma/causes-risks-prevention/risk-factors.html; *American Cancer Society*, "Hodgkin Lymphoma Risk Factors," available at https://www.cancer.org/cancer/hodgkin-lymphoma/causes-risks-prevention/risk-factors.html; *American Cancer Society*, "Non-Hodgkin Lymphoma Risk Factors," available at https://www.cancer.org/cancer/non-hodgkin-lymphoma/causes-risks-prevention/risk-factors.html.

43. In the absence of meeting this high threshold of asymptomatic screening guidelines, an individualized approach is necessary in determining which, if any, cancer screenings are appropriate for each patient. Even in the presence of a screening guideline, the potential benefits of screening must be weighed against the potential harms, which can vary depending on an individual's particular circumstances. Among the proposed class members, substantial variation is likely to exist in their baseline characteristics and underlying medical conditions. In addition, proposed class members may vary significantly in their total exposure to NDMA or NDEA, whether through dietary intake, environmental factors, or endogenous considerations, and use of affected valsartan is likely to be a relatively minor consideration as a risk factor. Therefore, the cancer risk from affected valsartan faced by each proposed class member, if any, may be low and highly uncertain. Given the variation across proposed class members in cancer risk from factors other than affected valsartan, uncertainty regarding whether affected valsartan increases cancer risks at all, and variation in preferences, it is likely that for the vast majority of proposed class members their historical use of affected valsartan would not affect the decision to screen for each type of cancer identified by plaintiffs.

44. While NDMA and NDEA exposure may be perceived as a potential general cancer risk, it has not been demonstrated as a risk with respect to any specific type of cancer, nor has the presence of nitrosamines in certain valsartan products been shown to present a general or specific cancer risk. This is particularly relevant when considering the USPSTF screening guidelines, which are with respect to specific types of cancers and population-specific considerations when determining the need to screen for each of those cancer types. In this matter, however, Plaintiffs

are proposing a class that would be screened for a wide range of cancers based on a single consideration and a single type of exposure without regard to other population factors and without demonstration of any specific cancer symptoms or exposure risk. Such a screening procedure would need to consider a far more complex array of individualized risk factors than presented for any individual cancer type considered by the USPSTF guidelines.

45. Furthermore, the USPSTF guidelines are, in fact, simply guidelines outlining general recommendations based on only a few, select factors, namely age and certain risks such as smoking. Guidelines are unable to make detailed recommendations tailored to each patient's numerous other considerations, for two important reasons. First, it is nearly impossible to pre-specify a population of patients based on a multitude of interacting risk factors; to have any semblance of accuracy in predicting risk given that risk associated with individual risk factors are often ascertained from separate populations of patients; and to expect physicians to comply with a complicated screening algorithm that has suspect scientific and clinical validity. Second, because of the first reason, the threshold of evidence—both in terms of scientific quality and in terms of clinical magnitude—for a given risk factor to define a population of patients for screening is necessarily very high. Notably, the guidelines do not recommend a package of procedures to screen for multiple types of cancers. Potential screening options are directly associated with a specific cancer type.

46. Additionally, to my knowledge, the guidelines to screen asymptomatic people have not been tailored any further based on exposure to NMDA or NDEA. For reasons I have described, this is entirely expected. As I discuss in **Section V.B**, there are other similarly documented factors that are potentially associated with increased cancer risk, such as gamma and X-radiation and ultraviolet rays from sunlight or exposure to known carcinogens such as asbestos. Many individuals in the general population are exposed to these factors, and exposure may differ across individuals. Yet, these risk factors have been deemed by expert committees not to rise to the level of evidence to warrant recommendations for additional cancer screening beyond what is outlined in the guidelines. While a behavior such as smoking does trigger additional recommended cancer screenings specific to lung cancer, nothing in the guidelines indicate that screening across all nine cancers specified by Plaintiffs is warranted due to exposure to NMDA

or NDEA and is further not appropriate for all patients given the many individualized factors considered in the decision to perform a certain screening procedure.

47. All of the guidelines and risk factors discussed above, including but not limited to those outlined in **Figure 2**, are considerations with significant relevance to the weighing of potential benefits of a screening program based on affected valsartan use against the many risks associated with such a program, as discussed in the next section.

B. Risks associated with medical screenings

48. Medical guidelines, such as the cancer screening guidelines I referenced in the previous section, balance the benefit from medical monitoring with the potential harm from these procedures. The overarching goal of cancer screening is to result in earlier and more effective treatments for patients to improve their health outcomes. However, cancer screening does not universally lead to better patient health or better outcomes. Overdiagnosis and false positives can result in increased and unnecessary follow-up testing, while negative screening results may result in false reassurance and may dissuade patients from self-monitoring signs and symptoms.[63] There are additional potential risks to some types of cancer screening procedures that can cause physical harm to patients. Professor Song fails to discuss any of the risks associated with the screening procedures they proposed. In **Figure 3**, I summarize the potential risks for the various screening options associated with the nine cancers identified by Plaintiffs.

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[63] *National Cancer Institute*, "Cancer Screening Overview (PDQ®)–Patient Version," August 19, 2020, available at https://www.cancer.gov/about-cancer/screening/patient-screening-overview-pdq. *See also*, *Cancer.net*, "Cancer Screening," January 2019, available at https://www.cancer.net/navigating-cancer-care/prevention-and-healthy-living/cancer-screening; *Centers for Disease Control and Prevention*, "What Are the Benefits and Harms of Screening?" August 23, 2021, available at https://www.cdc.gov/cancer/prostate/basic_info/benefits-harms.htm; *Centers for Disease Control and Prevention*, "Who Should Be Screened for Lung Cancer?" October 18, 2021, available at https://www.cdc.gov/cancer/lung/basic_info/screening.htm; *Centers for Disease Control and Prevention*, "What Is Breast Cancer Screening?," September 22, 2021, available at https://www.cdc.gov/cancer/breast/basic_info/screening.htm.

Figure 3. Associated risks with selected screening guidelines

Cancer Type	Selected Screening Options	Recommended Frequency	Potential Screening Risks
Colorectal	High-sensitivity gFOBT	Every Year	Follow-up (Colonoscopy); False-positives
	FIT and sDNA-FIT	Every 1-3 Years	Follow-up (Colonoscopy); False-positives
	Flexible Sigmoidoscopy (+ Annual FIT)	Every 5-10 years	Follow-up (Colonoscopy); Bleeding; Perforation
	Colonoscopy	Every 10 years	Hemorrhage; Perforation; Infection; Cardiopulmonary reaction
	CT Colonography	Every 5 years	Perforation[4]; Radiation; Follow-up (Colonoscopy)
Lung	Low-dose CT scan	Every Year	False-positives; Overdiagnosis; Radiation
	Sputum Cytology	Not Recommended	False-positives; Overdiagnosis
	Chest Radiography	Not Recommended	Radiation; False-positives
	Biomarker Measurement	Not Recommended	False-positives; Overdiagnosis
Pancreatic	CT Scan [7]	Not Recommended	Ionizing radiation; Reaction to IV contrast
	Endoscopic Ultrasound	Not Recommended	Complications relating to sedation; Bleeding or perforation; Follow-up risk (biopsy)
	MRI	Not Recommended	False-positives
Esophageal	Upper Endoscopy	-	Bleeding; Perforation; Overtreatment
Bladder	Urine Tests (Urinalysis, Cytology, Biomarkers)	No Recommendation	False-positives; Follow-up; Overtreatment
Liver	Serum alpha-fetoprotein	-	False-positives; Follow-up (liver biopsy)
	Ultrasonography	-	False-positives; Follow-up (liver biopsy)
Stomach	Upper Endoscopy	-	False-positives; Bleeding; Infection; Perforation; Overdiagnosis
Blood	Smear; CBC [5]	-	False results; Follow-up (bone marrow biopsy)
	Bone marrow biopsy [6]	-	Bleeding; Infection; Discomfort
Prostate	Prostate-specific Antigen (PSA)-based screening	No Standard / Every Two or More Years	False-positives; Follow-up (prostate biopsy); Overdiagnosis; Overtreatment; Treatment complications

Notes:

[1] Selected screening options and risks listed are described by the USPSTF's published recommendations or the NCI's PDQ database, unless otherwise noted with a reference in superscript.

[2] Recommended frequency defined by the USPSTF regarding population sub-groups for whom screening is recommended or guidelines have been published. The USPSTF does not provide a frequency recommendation for PSA-based prostate cancer screening, and the NCI states that no standard exists for asymptomatic patients. The American Urological Association notes that the screening interval should be two or more years. Carter, HB, *et al.,* "Early Detection of Prostate Cancer: AUA Guideline," *Journal of Urology*, Vol. 190, No. 2, 2013, pp. 419-426 at p.1.

[3] Blood cancers referenced are leukemia, myeloma, and lymphoma (Hodgkins and non-Hodgkins). "CBC" refers to Complete Blood Count.

Sources:

[1] *U.S. Preventive Services Task Force,* "Published Recommendations," available at https://www.uspreventiveservicestaskforce.org/uspstf/topic_search_results?topic_status=P.

[2] *National Cancer Institute*, "PDQ® - Cancer Information Summaries: Screening/Detection (Testing for Cancer)," available at https://www.cancer.gov/publications/pdq/information-summaries/screening.

[3] *U.S. Preventive Services Task Force*, "Screening for Prostate Cancer," *JAMA*, Vol. 319. No. 18, 2018, pp. 1901–1913.

[4] de Gonzalez, Amy Berrington, Kwang Pyo Kim, and Judy Yee, "CT Colonography: Perforation Rates and Potential Radiation Risks," *Gastrointestinal Endoscopy Clinics of North America*, Vol. 20, No. 2, April 2010, pp. 279–291.

[5] *Yale Medicine*, "Blood Cancers Fact Sheet," available at https://www.yalemedicine.org/conditions/blood-cancers.

[6] *Mayo Clinic*, "Bone Marrow Biopsy and Aspiration," available at https://www.mayoclinic.org/tests-procedures/bone-marrow-biopsy/about/pac-20393117.

[7] Poruk, Katherine E., Mathew A. Firpo, Douglas G. Adler, and Sean J. Mulvhill, "Screening for Pancreatic Cancer: Why, How, and Who?" *Annals of Surgery*, Vol. 257, No. 1, January 2013, pp. 17–26, at p. 8.

49. As medical screenings are not riskless, healthcare providers take these risks into consideration before recommending screening procedures. Overdiagnosis occurs when a screening test detects a condition that would not have resulted in health problems or falsely detects a condition that in fact does not exist. False positives occur when a screening test suggests cancer is present when in fact it is not. Furthermore, many other patients may have a condition that does not warrant medical treatment, either because the existence of the condition does not imply a significant difference in life expectancy or quality of life or because a treatment that is safe and effective enough to treat asymptomatic disease does not exist. In general, excess use of screening in those cases can result in overtreatment that can potentially be harmful to patients and result in unnecessary pain, stress, disruption, and/or expenses.

50. As an example, prostate cancer screening tests for elevated levels of prostate-specific antigen ("PSA") in the blood. However, such metrics can be unreliable, and a study on prostate-cancer diagnosis found that up to 75% of positive PSA tests are a false-positive result.[64] This means that a recommendation to screen patients in this population would subject 75% of the patients

[64] Gilbert, Natasha, "The pros and cons of screening," *Nature*, March 25, 2020, available at https://www.nature.com/articles/d41586-020-00841-8. *See also*, Kasivisvanathan, Veeru, *et. al.*, "MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis," *The New England Journal of Medicine*, Vol. 378, No. 19, May 10, 2018, pp. 1767–1777.

with positive PSA tests to unnecessary harm, as they do not have cancer at all. An additional set of patients may have prostate cancer, but may not be warranted for further treatment, due to the nature of their cancer, their other comorbidities, and their preferences for potentially ineffective treatment.

51. False positives can also lead to unnecessary follow-up tests and treatments, causing additional risk and harm. A positive PSA test is often followed by a prostate biopsy, which is an invasive procedure that carries a significant risk of complications such as infection.[65] Similarly, the typical follow-up procedure to a positive stool test for colorectal cancer is colonoscopy.[66] Colonoscopies carry the risk of serious bleeding events, perforation, and cardiopulmonary events during sedation.[67] Once a screening test is done, clinicians and patients may be sent down pathways that incur these potentially needless or harmful procedures. Therefore, it is paramount to think carefully before recommending any screening test for a population of patients. The relatively few risk factors that make it into cancer screening guidelines demonstrates the high caution that expert panels take in including risk factors into population recommendations.

52. As a general point, no screening test is completely accurate. Screening tests will in general falsely classify patients with the disease as not having the disease (i.e., false negative in the Classification Matrix in **Figure 4**) at a certain rate, and they will also falsely classify patients without the disease as having the disease (i.e., false positive in the Classification Matrix in **Figure 4**) at a certain rate. For any screening test, technicians, clinicians, and policymakers must determine a "threshold" above which the screening test is "abnormal" and suggestive of further scrutiny or treatment. In general, the lower the baseline risk of the population being screened, the higher this threshold will be, because otherwise, the screening test will subject too many patients to false positives. However, as the threshold is raised, patients who are at

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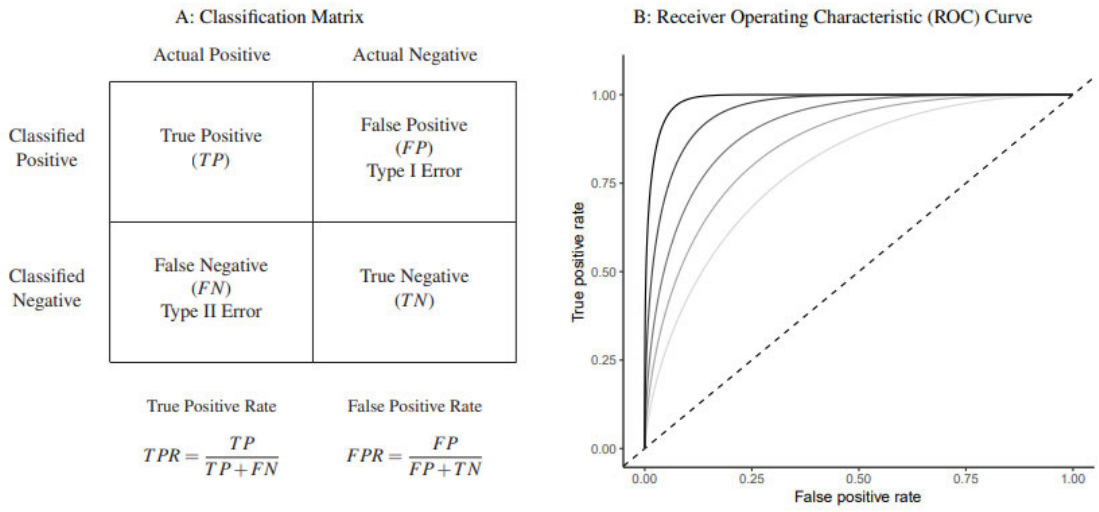
[65] Loeb, Stacy, *et al.,* "Systematic Review of Complications of Prostate Biopsy," *European Urology*, Vol. 64, No. 6, December 2013, pp. 876–892.

[66] *Centers for Disease Control and Prevention*, "Colorectal Cancer Screening Tests," February 8, 2021, available at https://www.cdc.gov/cancer/colorectal/basic_info/screening/tests.htm.

[67] *U.S. Preventive Services Task Force JAMA*, "Screening for Colorectal Cancer," May 18, 2021, pp.1965–1977, at p. 1974.

higher risk will be subjected to false negatives. This implies an important point: unnecessarily expanding the pool of patients to be screened will harm patients who are truly at risk for cancer by inducing more false negatives for these patients. In other words, implementing a screening program for patients who have taken affected valsartan may induce a harmful externality on patients who are genuinely at risk by causing patients who actually have cancer to be misdiagnosed (i.e., undiagnosed).[68]

Figure 4. Classification matrix and ROC curve [69]



53. Furthermore, recent literature has investigated and identified the issue of "scrutiny-dependent" cancers, which are ones where the harder physicians look, the more cases they find.[70] Many of

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[68] This framework is further illustrated in Panel B of **Figure 4**. **Figure 4** provides examples of the Receiver Operating Characteristic ("ROC") curves, which emphasize the relationship between the true positive rate ("TPR") and the false positive rate ("FPR"). As I explained, an unnecessary expansion of the pool of the patients that are screened will increase the false negative rate. This in-turn will decrease the true positive rate (see the formula for TPR in Panel A). Consequently, the ROC curve will shift inward, from a darker to a lighter curve, suggesting a less reliable screening that is less likely to identify patients who are truly at risk for cancer. *See, e.g.,* National Cancer Institute, "Cancer Screening Overview (PDQ®)-Health Professional Version," June 2021, available at https://www.cancer.gov/about-cancer/screening/hp-screening-overview-pdq.

[69] Chan, David C, *et al.,* "Selection with Variation in Diagnostic Skill: Evidence from Radiologists," *National Bureau of Economic Research*, November 2019, available at https://www.nber.org/system/files/working_papers/w26467/w26467.pdf at p. 40.

[70] Begley, Sharon, "Too much screening has misled us about real cancer risk factors, experts say," *STAT*, January 1, 2018, available at https://www.statnews.com/2018/01/01/cancer-screening-misled-risk-factors/. *See also*, Welch, Gilbert H., and Otis W. Brawley, "Scrutiny-Dependent Cancer and Self-fulfilling Risk Factors," *Annals of Internal Medicine*, Vol. 168, No. 2, January 16, 2018, pp. 143–144.

these scrutiny-dependent cases do not imply any significant impact on life expectancy or quality of life because they may involve cancers that are slow-growing or occur in a population with other competing considerations for mortality and quality of life.[71] Examples of scrutiny-dependent cancers include prostate, breast, thyroid, and lung cancers. While past increases in screening for these cancers initially seemed beneficial, more recent increases in screening for these cancers have resulted in an increase in diagnoses but have no associated reduction in mortality.[72] In the example of prostate cancer, one study in 2000 compared prostate-cancer incidence and mortality in the United States, where screening is common, and the United Kingdom, where it is not, and found that while additional screening in the United States substantially increased the number of people diagnosed with prostate cancer, it did not result in lower mortality than in the United Kingdom.[73] Additionally, a 2016 study found that the risk of prostate cancer in men due to family history has been overestimated by nearly half since men with a family history of prostate cancer are more deeply scrutinized and screened for prostate cancer.[74] In the example of breast cancer, a 2017 study found that women in higher educated and higher income neighborhoods were twice as likely to be diagnosed with breast cancer, probably due to greater access to the health care system and therefore to mammograms, breast ultrasounds, and MRIs.[75] A separate study estimated that about half of breast cancers

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71 Begley, Sharon, "Too much screening has misled us about real cancer risk factors, experts say," *STAT*, January 1, 2018, available at https://www.statnews.com/2018/01/01/cancer-screening-misled-risk-factors/. *See also*, Welch, Gilbert H., and Otis W. Brawley, "Scrutiny-Dependent Cancer and Self-fulfilling Risk Factors," *Annals of Internal Medicine*, Vol. 168, No. 2, January 16, 2018, pp. 143–144.

72 Gilbert, Natasha, "The pros and cons of screening," *Nature*, March 25, 2020, available at https://www.nature.com/articles/d41586-020-00841-8.

73 Oliver, Steven E., *et al.,* "Comparison of Trends in Prostate-Cancer Mortality in England and Wales and the USA," *The Lancet,* Vol. 355, No. 9217, May 20, 2000, pp. 1788–1789, as cited in Gilbert, Natasha, "The pros and cons of screening," *Nature*, March 25, 2020, available at https://www.nature.com/articles/d41586-020-00841-8.

74 Tangen, Catherine M., *et al.*, "Biases in Recommendations for and Acceptance of Prostate Biopsy Significantly Affect Assessment of Prostate Cancer Risk Factors: Results From Two Large Randomized Clinical Trials." *Journal of Clinical Oncology*, Vol. 34, No. 36, December 20, 2016, pp. 4338–4344.

75 Conroy, Shannon M, *et al.,* "Racial/Ethnic Differences in the Impact of Neighborhood Social and Built Environment on Breast Cancer Risk: The Neighborhoods and Breast Cancer Study." *Cancer Epidemiology and Prevention Biomarkers,* Vol. 26, No. 4, 2017, pp. 541–552. *See also*, Begley, Sharon, "Too much screening has misled us about real cancer risk factors, experts say," *STAT*, January 1, 2018, available at https://www.statnews.com/2018/01/01/cancer-screening-misled-risk-factors/.

detected through screening were over-diagnosed and would not have led to problems or required treatment.[76]

54. As another example, excess scrutiny can even affect a traditionally aggressive cancer such as lung cancer. In Japan, a prevalence screen using computed tomography found almost 10 times as much lung cancer as they had previously found in the same population using chest X-rays, and the risk of lung cancer detection was virtually the same in smokers and never-smokers, despite a plethora of evidence showing that the risk of dying of lung cancer is at least 15 times higher in smokers than never-smokers.[77] In this case, additional screening weakened a genuine high-risk factor.[78] A separate Mayo clinic randomized trial showed a 51% risk that a chest x-ray and/or sputum cytology-detected cancer represented overdiagnosis.[79]

55. Given the potential for serious risks associated with cancer screenings, healthcare providers assess the benefit-risk tradeoffs and make decisions regarding the appropriateness of cancer screenings based on individual patient factors. The general medical monitoring program, including the single set of six monitoring services considered by Professor Song in his class-wide methodology, would not appropriately apply to all proposed class members and could cause harm to many patients.

V. PROFESSOR SONG'S ANAYLSIS FAILS TO ADDRESS INDIVIDUALIZED ISSUES RELATED TO MEDICAL MONITORING

56. A single monitoring program design does not apply to all proposed class members due to heterogeneity in patient risk of developing cancer from affected valsartan exposure and variation in other factors that may affect patient risks of cancer. A single program to monitor

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[76] Miller, Anthony B., *et al.,* "Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial," *BMJ*, Vol. 348, February 11, 2014.

[77] Welch, Gilbert H., and William C. Black, "Overdiagnosis in Cancer," *Journal of the National Cancer Institute*, Vol. 102, No. 9, May 5, 2010, pp. 605–613, at p. 608.

[78] Welch, Gilbert H., and Otis W. Brawley, "Scrutiny-Dependent Cancer and Self-fulfilling Risk Factors," *Annals of Internal Medicine*, Vol. 168, No. 2, January 16, 2018, pp. 143–144, at p. 144.

[79] Welch, Gilbert H., and William C. Black, "Overdiagnosis in Cancer," *Journal of the National Cancer Institute*, Vol. 102, No. 9, May 5, 2010, pp. 605–613, at p. 608.

for all the cancers outlined by the Plaintiffs would likely impose unacceptable harms on many proposed class members and provide little or no benefit. Some proposed class members may be at low risk and never require cancer screening as a result of their use of affected valsartan and other patient-specific risk factors, while others may receive widely varying screening procedures dependent on their specific risk profile, and still other proposed class members may receive cancer screening driven by better-established factors addressed by clinically supported medical guidelines and wholly unrelated to their use of affected valsartan.

57. While I will comment on the services that Professor Song considers in his "common methodology" more below, it is notable that Dr. Kaplan, one of the other Plaintiffs' experts, identifies different screening procedures from the ones considered by Professor Song in the proposed monitoring program for these nine cancers.[80] Dr. Kaplan's recommendations share similar flaws to Professor Song's "common methodology," insofar as they do not properly account for the variation in risk among the proposed class members and his recommendations do not fully account for the relative benefits and harms of screening as recommended by widely accepted medical guidelines. Indeed, the fact that Dr. Kaplan's recommendations differ from Professor Song's further reinforces the hazards of departing from evidence-based medical guidelines to construct indiscriminate multi-cancer screening programs without accounting for the patient-specific, cancer-specific, and population-specific risk factors that actually drive screening recommendations made by individual doctors to individual patients in real-world clinical practice.

58. Dr. Kaplan himself acknowledges the need for providers to make clinically appropriate decisions based on the medical history of a given patient. For example, Dr. Kaplan recommends an upper endoscopy every five years or "based on symptoms, smoking and alcohol history," and an annual low dose CT chest scan "especially in smokers or prior

[80] Dr. Kaplan's proposed program includes: (1) an annual physical with lab tests that includes a blood smear evaluation (CBC), a basic chemistry profile ("CMP") including liver enzymes, kidney function, labs for general signs of inflammation or imbalances, thyroid function tests, PSA (for males), and urinalysis, (2) an annual Galleri blood test or similar liquid biopsy, (3) an annual Cologuard or similar fecal testing, (4) an annual low-dose CT chest scan, (5) a colonoscopy every 5 years, and (6) an upper endoscopy every 5 years. Kaplan Report, p. 4.

smokers."[81] Dr. Kaplan's attempt to incorporate some flexibility into his approach acknowledges the reality that cancer screening decisions cannot be separated from patient-specific considerations, yet at the same time renders his approach unworkable to the extent it is intended to provide clear, consistent, population-based recommendations for the entire population of proposed class members.

59. The basic problem remains the same for Professor Song and Dr. Kaplan: both are trying to craft a top-down approach to cancer screening that imposes a clinically inadvisable multi-cancer screening program without accounting for the individualized, multi-factor considerations and professional judgments that actually drive screening decisions through doctor-patient relationships. Thus, both Professor Song and Dr. Kaplan depart, albeit in different directions and by varying degrees, from the individualized model of patient care that has always governed and should continue to govern cancer screening.

60. Separately, several of the screening methods Dr. Kaplan suggests, such as the blood test Galleri and stool DNA test Cologuard, are not widely recommended due to their lack of specificity and accuracy or have not yet been evaluated as part of large-scale screening programs. Additionally, the Galleri test is a new technology that has not been evaluated under the published guidelines of the USPSTF and is not FDA approved. Finally, it "is not covered by insurance."[82]

61. While Dr. Kaplan does caveat the clinical appropriateness of certain screenings in particular circumstances, his approach replaces the default guideline recommendation not to screen asymptomatic patients with a default recommendation to screen and fails to provide a meaningful guiding principle to articulate the specific circumstances he identifies in which individual patient-specific variables might intervene to alter his recommendations. Professor Song, by contrast, does not acknowledge any variation or the many ways in which the need for medical monitoring services would vary across proposed class members. Instead, Professor

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[81] Kaplan Report, p. 4.

[82] "Currently, the Galleri test is not covered by insurance… GRAIL is actively pursuing coverage from various sources; however, this process takes time." *Galleri*, "Frequently asked questions for patients about the Galleri test," available at https://www.galleri.com/support/faqs.

Song simply provides "an example of an initial core set of medical services that patients with an increased risk of cancer could benefit from, to which additional services that are deemed appropriate for this class of patients may be added."[83] Furthermore, Professor Song attributes the need for all medical monitoring services to the use of affected valsartan, does not consider the fact that no medical guidelines or clinical evidence support screening on the basis of this single factor in the absence of other patient-specific, cancer-specific, or population-specific risk factors, and does not consider the fact that many proposed class members may have received cancer screening even in the absence of any affected valsartan use, while others are not recommended for cancer screening regardless of affected valsartan use.

62. In practice, healthcare providers recommend cancer screenings that are relevant for a given patient based on their unique circumstances, including patient and family histories, lifestyle, age, preferences for treatment, and many other factors. To the extent nitrosamine exposure is deemed a relevant consideration by a particular healthcare provider, it is highly unlikely that for most patients such a judgment would be driven by a patient's affected valsartan use alone. Instead, the decision to screen may consider exposure to NDMA and NDEA through other dietary, environmental, or endogenous sources, together with exposure to other potentially carcinogenic agents. For example, Professor Song recognizes that "life expectancy and the development of medical conditions … may render the monitoring program less appropriate clinically,"[84] but he does not make the connection that a single monitoring program design based on a single-factor exposure would be at odds with this important clinical observation. Rather, Professor Song asserts without basis that the patient population "would be more likely to be stable in its composition" in the initial years of the monitoring program.[85] This assumption ignores the variability in patients' current health status, starting with the patients' medical history, comorbidities, family history, lifestyle, age, and other risk factors, with

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[83] "For the purposes of this report, I assume in this section that the foundation of such a potential monitoring program could begin with the following services: a urinalysis on an annual basis, a complete blood count on an annual basis, an evaluation and management (office visit) on an annual basis, a low-dose computed tomography (CT) chest imaging test on an annual basis, an upper endoscopy every five years, and a screening colonoscopy every five years." Song Report, ¶32.

[84] Song Report, ¶39.

[85] Song Report, ¶39.

exposure to NDMA or NDEA through diet, environment, endogenous factors, or affected valsartan use, to the extent considered at all, falling distantly behind these primary considerations when considering the advisability of screenings.

63. In this section, I outline some of the key variation among patients that would result in different clinical decisions with respect to cancer screening for different members of the proposed class. In many cases, there would be no change in the screening decision based on affected valsartan usage—many of the proposed class members would have had their physicians recommend for or against cancer screening for reasons unrelated to their affected valsartan use.

A. Factors other than affected valsartan use are far more important considerations in the individualized judgment whether to recommend cancer screening

64. Professor Song's analysis fails to acknowledge that there are many patient characteristics based on their individual medical history, lifestyle, and underlying conditions that are far more clinically significant in determining whether cancer screening is appropriate or whether cancer screening would have been recommended regardless of affected valsartan use. As discussed in **Section IV.A**, well-established medical guidelines have expressed the limited circumstances under which screening may be indicated for specific cancers in specific populations based on patient-specific, cancer-specific, and population-specific risk factors. These medical guidelines do not recommend multi-cancer screenings on an indiscriminate basis due to a single exposure factor that is not strongly linked to a particular type of cancer.

65. The simple reality is, in real-world patient care, considerations other than affected valsartan use are far more important to the judgments made by healthcare providers and their patients in deciding whether screening for a particular cancer risk is recommended. Indeed, patients who are prescribed valsartan may already have an increased risk of cancer prior to taking affected valsartan, as patients with hypertension are likely to be older or have other comorbidities.[86] A review of studies sampling patients prescribed valsartan as a second-line therapy for

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[86] Buford, Thomas W., "Hypertension and Aging," *Ageing Research Reviews*, Vol. 26, March 2016, pp. 96–111. *See also*, Seretis, Aristeidis, *et al.,* "Association between blood pressure and risk of cancer development: a systematic review and meta-analysis of observational studies," *Scientific Reports*, Vol. 9, No.1., June 2019, pp. 1–12, at pp. 5–6.

hypertension found the average age to be 63.3 years and that about a quarter of the population had diabetes.[87] Baseline characteristics of patients in one of the largest clinical trials of valsartan included an average rate of smoking above 26 percent and a rate of diabetes mellitus of about 30 percent.[88] Generally, age is considered the most important risk factor for cancer.[89] There is also a "very likely causal association" between type-2 diabetes and the incidence of liver, pancreatic, and endometrial cancer.[90]

66. Additionally, I reviewed the publicly available Medical Expenditure Panel Survey ("MEPS") data, which conducts large-scale surveys of families and individuals, their medical providers, and employers. It provides "the most complete source of data on the cost and use of health care and health insurance coverage."[91] I focused my review of these data on the surveys between 2012, the start of the period at-issue, and 2019, the last survey year available.

67. I found substantial variation in the MEPS data across the individuals who took affected valsartan, which would need to be accounted for on an individualized basis to better understand what monitoring services they might undergo. For example, the ages of the 630 patients who took affected valsartan between 2012 and 2019 and did not have cancer, ranged from 24 to 85.[92] A subset of these patients also reported that they smoked (approximately 12.6 percent of the patients who were asked the question), but the durations and frequency of their smoking

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87 Abraham *et. al.*, "Real-world effectiveness of valsartan on hypertension and total cardiovascular risk: review and implications of a translational research program," *Vascular Health Risk Management,* Vol. 7, March 2011, pp. 209–235, at p. 213.

88 Rates of smoking and diabetes mellitus were similar across treatment and control groups. Julius, Stevo, *et al.,* "The Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) Trial: Outcomes in Patients Receiving Monotherapy," *Hypertension,* Vol. 48, No. 3, September 2006, pp. 385–391, at p. 387.

89 *National Cancer Institute*, "Age and Cancer Risk," March 5, 2021, available at https://www.cancer.gov/about-cancer/causes-prevention/risk/age.

90 Ling, Suping, *et al.*, "Association of Type 2 Diabetes With Cancer: A Meta-analysis With Bias Analysis for Unmeasured Confounding in 151 Cohorts Comprising 32 Million People," *Diabetes Care*, Vol. 43, September 2020 pp. 2313–2322, at p. 2321.

91 MEPS data (Household Full Year Population Characteristics File, Household Full Year Medical Conditions File, and Household Prescribed Medicines Event File).

92 The MEPS data include NDC information for prescription drugs. Affected valsartan is identified based on NDCs in the FDA's Recalled NDC List (the MEPS data does not contain information on lot numbers). *See* FN 23.

still needs to be determined on an individual basis.[93] The variation between these patients would likely be even more pronounced based on all the patient characteristics that a healthcare provider would review in assessing whether to recommend cancer screening for an individual patient.

68. In addition, I compared patients who took affected valsartan, patients who took non-affected valsartan, and patients who did not take valsartan between 2012 and 2019.[94] I found that the rate of cancer and diabetes in the MEPS data for individuals who took affected valsartan (34.8 percent for diabetes and 20.2 percent for cancer) was similar to the rate for the individuals who took non-affected valsartan (38.2 percent for diabetes and 19.1 percent for cancer). However, the rate of these diseases was substantially lower for patients who did not take valsartan (16.4 percent for diabetes and 12.8 percent for cancer). This evidence suggests that, at least with respect to some risk factors, patients taking valsartan are more likely to have risk factors related to cancer than other patients, and may be more likely to be screened for cancer irrespective of whether or not they took affected valsartan.

69. In general, valsartan is indicated for use for the treatment of patients with hypertension, or a history of heart failure or post-myocardial infarction.[95] Each of these pre-existing conditions is a significant risk factor for mortality and may impact quality of life. As I mentioned above, these would be relevant considerations in the decisions to screen for or treat cancer. Hypertension has a large and statistically significant and positive association with kidney,

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[93] The rate of smoking is based on the subset of patients who were asked this survey question. 612 of the 630 patients who took affected valsartan were asked if they smoked. Survey questions (i.e., "ADSMOK42" and "OFTSMK53") varied slightly over the years. Patients that reported to be a current smoker, to smoke every day, or to smoke some days were considered smokers. *See e.g.,* MEPS codebook for 2016 available at: https://meps.ahrq.gov/mepsweb/data_stats/download_data_files_codebook.jsp?PUFId=H192.

[94] A patient is classified as taking affected valsartan if they had at least one affected valsartan NDC from the FDA's Recalled NDC List (787 patients). Those patients classified as taking non-affected valsartan had a least one valsartan prescription (based on "rxdrgnam"), but no prescriptions for affected valsartan (912 patients). All other patients (patients who did not take any valsartan product) had at least one drug prescription (105,861 patients). Cancer rates are calculated based on those individuals that responded to the question (that is, the response is not "Inapplicable"). Cancer is identified based on "cancerdx" in the Full Year Population Characteristics files. Diabetes rates are calculated based on patients older than 17 years old. Diabetes is identified in the Medical Conditions files (i.e., "ICD9CODX" = "250" or "ICD10CDX" = "E11").

[95] *Novartis*, "Diovan (valsartan)," August 2005, pp. 3–18, at pp. 9–10 available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021283s011lbl.pdf.

colorectal, and breast cancer; smaller but statistically significant associations between hypertension and endometrial, liver, and esophageal cancer have also been documented. [96] A history of heart failure is also associated with a subsequent significant increased incidence of cancer, including cancer of the respiratory organs, breast, urinary tract, and pharynx.[97] Myocardial infarction is associated with an increased risk of overall cancer, even after adjusting for pre-existing conditions such as hypertension, diabetes, and socioeconomic status.[98] These types of individualized considerations—age, comorbidities, lifestyle, and other risk factors—are far more likely drivers of the recommendation to screen or not screen for a particular type of cancer in a given individual than the possibility of an unverified marginal increased risk of cancer from taking affected valsartan.

1. Patients undergoing screening procedures based on any of the numerous factors other than affected valsartan use would not incur additional costs

70. Determining which patients would receive different types of cancer screening irrespective of affected valsartan use, and which patients would receive incremental additional screening due to affected valsartan use requires individualized assessment. Professor Song's analysis does not account for such considerations in estimating the potential healthcare spending accrued from medical monitoring.

71. Many of the proposed class members would receive the screenings specified by Professor Song for reasons unrelated to the intake of affected valsartan. Such reasons would include medical and family history, genetic factors, and lifestyle. For example, patients with a family history of the genetic disorder Familial Adenomatous Polyposis ("FAP") are recommended regular colorectal cancer screening via colonoscopy beginning at a young age.[99] In the MEPS data, out

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[96] Seretis, Aristeidis, *et al.,* "Association between blood pressure and risk of cancer development: a systematic review and meta-analysis of observational studies," *Scientific Reports*, Vol. 9, No. 1, June 2019, pp. 1–12, at pp. 5–6.

[97] Roderburg, Christoph, *et al.*, "Heart failure is associated with an increased incidence of cancer diagnoses," *ESC Heart Failure*, Vol. 8, No. 5, 2021, pp. 3628–3633, at p. 3631.

[98] Malmborg, Morten, *et al.,* "Incidence of new onset cancer in patients with a myocardial infarction – a nationwide cohort study," *BMC Cardiovascular Disorders,* Vol. 18, No. 1, October 2018, pp. 1–9, at p. 3.

[99] Because patients with FAP have a lifetime risk of colorectal cancer approaching 100%, those with a personal history of FAP are recommended surgical intervention. Screening guidelines for patients without FAP but a

of the 128 patients who took an affected valsartan in 2018, were 50 years or older, and were asked whether they had a colonoscopy, 74.2 percent reported that they received a colonoscopy in the past 10 years.[100] These patients, therefore, may not require an additional colonoscopy for some time, and there would be no incremental cost associated.[101]

72. Additionally, based on the 2018 MEPS survey, approximately 10 percent of patients refused to undergo a colonoscopy screening that was offered to them.[102] This evidence suggests that a portion of the proposed class members may also refuse to undergo monitoring services that are offered to them. Professor Song's analysis does not account for proposed class members who would opt out of any proposed monitoring program and therefore should not be included in his healthcare spending estimate.

73. Furthermore, a procedure such as a urinalysis can be administered to screen or diagnose other clinical issues, and proposed class members could have received a urinalysis for other routine care and not for bladder cancer specifically. In these cases, there is no incremental cost associated with the screenings because they would have happened regardless of affected valsartan use. As demonstrated in **Figure 5** below, I found that 14.0 percent of patients who took affected valsartan received a urinalysis within just one year of their first observed affected

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family history vary depending on a patient's individual genetic test results. Specifically, those with a known disease-causing mutation and those who have not undergone genetic testing are both recommended annual colonoscopy beginning at the age of 10 to 15 years; however, patients who have not undergone genetic testing are advised to gradually reduce screening frequency over time, and to eventually follow average-risk guidelines after the age of 50. Meanwhile, those patients with negative genetic test results are recommended the same colorectal cancer screening as average-risk patients. Aihara, Hiroyuki, *et al.,* "Diagnosis, surveillance, and treatment strategies for familial adenomatous polyposis: rationale and update," *European Journal of Gastroenterology & Hepatology*, Vol. 26, No. 3, 2014, pp. 255–262, at 256, available at https://doi.org/10.1097/MEG.0000000000000010.

[100] There are 142 patients who took affected valsartan in 2018 (the last survey year with a colonoscopy screening indicator for individuals older than 50 years), did not report developing cancer ("cancerdx" in the Full Year Population Characteristics files), and were 50 years or older. Out of those patients 14 did not have a valid response to the colonoscopy screening question ("ADCLNS42" in Full Year Population Characteristics). See footnotes 23 and 92.

[101] As outlined in **Figure 3**, a colonoscopy for colorectal cancer screening is recommended every 10 years.

[102] Based on the 2018 MEPS survey (latest year of survey with this question), 9,307 out of 30,461 patients were asked if they had a colonoscopy in the past 10 years. Of those asked, 980 indicated that they were offered but refused. *See* Medical Expenditure Panel Survey, Longitudinal Data Codebook, available at: https://meps.ahrq.gov/mepsweb/data_stats/download_data_files_codebook.jsp?PUFId=H209&varName=ADCLNS42.

valsartan prescription in the OptumHealth data.[103] Similarly, 30.1 percent of patients who took affected valsartan received a complete blood count ("CBC") within one year of their first observed affected valsartan prescription. These patients would therefore not need additional CBC or urinalysis procedures and would not incur any incremental costs. Unsurprisingly, only a small percent of these patients received more invasive monitoring procedures such as an esophagogastroduodenoscopy or colonoscopy.

Figure 5. Percent of patients undergoing Professor Song's procedures within one year of first affected valsartan prescription

CPT/HCPCS Code	Percent of Patients
81001 (Urinalysis)	**14.0%**
85025 (Complete Blood Count)	**30.1%**
99214 (30-39 Minute Office Visit)	**73.5%**
43235 (Esophagogastroduodenoscopy)	**0.6%**
G0121 (Colonoscopy)	**0.5%**

Notes:

[1] Affected valsartan subject to recall are identified by the FDA by NDC and manufacturing lot number. This analysis uses the FDA's NDC Recalled List to determine affected valsartan products as manufacturing lot numbers are not available in the data. See footnote 23.

[2] This analysis includes 51,183 patients who had a prescription for at least one affected valsartan from January 1, 2012 (beginning of the at-issue period) through March 31, 2017 (end of data availability), and twelve months of continuous eligibility before their first affected valsartan prescription.

[3] The analysis looks at the year preceding a patient's first affected valsartan prescription to assess the utilization of the screening procedure proposed by Professor Song.

[4] Low-dose chest CT scan procedures are not included in the analysis because code 71271 was introduced in 2021 and its parent code, G0297, had inconsistent use across the analyzed years.

Source: OptumHealth data.

[103] The OptumHealth database contains healthcare utilization records of over 19 million beneficiaries (including employees, spouses, dependents, and retirees) with commercial insurance from over 80 large, self-insured Fortune 500 companies for the period Q1 1999 through Q1 2017. The companies represented in the data operate in a broad range of industries (including manufacturing, telecommunications, financial services, and food and beverage) with locations in all Census areas of the U.S. The database contains information on patient age, gender, enrollment history, medical diagnoses, procedures performed, dates and place of service, prescription drug use, and payment amounts.

74. [redacted][104] [redacted][105] [redacted][106]

75. [redacted][107] [redacted][108] [redacted]

76. Many proposed class members may already be receiving cancer screenings based on individual reasons including their medical and family history, others may be receiving the specific

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104 Deposition of John Judson, February 8, 2021 ("Judson Deposition"), Exhibit 0001 p.3, Exhibit 0003 at 0004.

105 Judson Deposition, 17:7–18:1, 45:15–45:24; 194:2–194:22.

106 Judson Deposition, 194:2–197:15.

107 Deposition of Paulette Silberman, March 22, 2021 ("Silberman Deposition"), Exhibit PS0001, pp.2–4, 36.

108 Silberman Deposition, 54:21–55:1, 93:18–24, Exhibit PS0001.

109 Silberman Deposition, 75:1–25, 93:18–24, Exhibit PS0001.

procedures proposed by Professor Song for reasons other than cancer screening, and still others may simply opt out of undergoing any offered procedures. In all of these cases, these proposed class members would not incur any additional cost for the procedures proposed by Professor Song for a medical monitoring program. Determining which of these proposed class members would not need or want to undergo the offered procedures for various reasons is individualized.

2. Individual patient characteristics could contraindicate patients from screening

77. As discussed above, the decision to recommend screening is highly individualized, and many patient factors are far more important than NDMA and NDEA exposure for a healthcare provider in making that decision. Even if NDMA and NDEA exposure were deemed a potential consideration for some patients in some populations, for many proposed class members, medical monitoring could be deemed contraindicated by their healthcare providers based on other, more clinically significant factors. For example, proposed class members may have underlying conditions that preclude them from screening and thus, would not be subject to medical monitoring; proposed class members may be too old for effective cancer treatments and thus, might not be subject to medical monitoring; and proposed class members may face more harm than benefits from the medical monitoring.

78. [redacted][110][redacted][111][redacted][112][redacted]

[110] Deposition of Sarah Zehr-Johnson, May 20, 2021 ("Zehr-Johnson Deposition"), Exhibit SZ0001, pp. 2–3.

[111] Zehr-Johnson Deposition, 50:14–25, 52:1–4.

[112] Zehr-Johnson Deposition, 55:15–24.

[redacted].[113]

79. [redacted][114] [redacted].[115] [redacted]

80. [redacted][116] [redacted]

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[113] *National Cancer Institute*, "Many Older Adults Screened Unnecessarily for Common Cancers," August 27, 2020, available at https://www.cancer.gov/news-events/cancer-currents-blog/2020/screening-cancer-older-adults-unnecessary.

[114] [redacted] Deposition of Robert Kruk, May 12, 2021, 83:1–83:4, 90:10–90:18, Exhibit RK0001, pp. 2–3, 20–31.

[115] *U.S. Preventive Services Task Force JAMA*, "Screening for Prostate Cancer," Vol. 319, No. 18, May 8, 2018, pp. 1901–1913, at 1901, 1904.

[116] Deposition of Roger Tasker, May 6, 2021 ("Tasker Deposition"), Exhibit RT0002, pp.2–3.

[redacted][117][redacted][118][redacted][119][redacted].

81. Determining whether a patient should proceed with cancer screening and whether that screening would be more beneficial than harmful is a largely individualized decision. As mentioned previously, to the best of my knowledge, there do not exist guidelines for screening multiple types of cancer. Rather, when screening guidelines do exist, they recommend screening for specific types of cancers in a well-defined population that is at a substantially higher risk. Not only is this a patient-by-patient decision, but it is also a decision for each type of cancer. Therefore, even conditional on proceeding with some screening, the specific services needed as part of a medical monitoring program would again vary across patients. To summarize, from a clinical perspective, a provider will not recommend a cancer screening if the risks outweigh the benefits for a given patient based on that patient's individual circumstances.

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117 *U.S. Preventive Services Task Force*, "Pancreatic Cancer: Screening," August 6, 2019, available at https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/pancreatic-cancer-screening#fullrecommendationstart.

118 [redacted] Tasker Deposition, 50:4–50:22, Exhibit RT0002, pp. 16–17, 20.

119 Pietrangelo, Ann, "What You Should Know About PSA Levels After Prostatectomy," *Healthline*, September 18, 2018, available at https://www.healthline.com/health/prostate-cancer/psa-after-prostatectomy.

B. Exposure to potential carcinogens varies by patient

82. To the extent exposure to potential carcinogens may be one consideration of many in the cancer-screening decision for an individual patient, Professor Song also fails to recognize that patients vary in terms of their exposure to potential carcinogens, which would affect their need, if any, for medical screening. Carcinogens are substances and exposures that can lead to one or a host of cancer(s).[120] Smoking, for example, can cause cancer almost anywhere in the body, including the lungs—one of the specified cancers in this matter.[121] In December 2021, the U.S. Department of Health and Human Services released its 15th report on carcinogens, which listed 256 agents, substances, mixtures, and exposure circumstances that are known (63 of the 256) or reasonably anticipated (193 of the 256) to cause cancer in humans.[122] NDMA and NDEA are listed among the 193 items reasonably anticipated to be human carcinogens.[123] Some of the known carcinogens are prevalent in exposure across the population. For example, an estimated 34.1 million adults (or 14 percent of adults) in the U.S. smoked cigarettes in 2019 and about 1.3 million U.S. workers were at risk of exposure to asbestos in 2021.[124]

83. People can be exposed to carcinogens through a wide range of environmental factors such as: lifestyle factors (e.g., nutrition, tobacco and alcohol use, physical inactivity), naturally

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120 *American Cancer Society*, "Determining if Something Is a Carcinogen," May 17, 2019, available at https://www.cancer.org/cancer/cancer-causes/general-info/determining-if-something-is-a-carcinogen.html. *See also*, *International Agency for Research on Cancer*, "List of classifications by cancer sites with *sufficient* or *limited evidence* in humans, IARC Monographs Volumes 1-130," December 8, 2021, available at https://monographs.iarc.who.int/wp-content/uploads/2019/07/Classifications_by_cancer_site.pdf.

121 Including the blood, bladder, cervix, colon and rectum, esophagus, kidney and renal pelvis, larynx, liver, lungs, trachea and bronchus, mouth and throat, pancreas, and stomach. *Centers for Disease Control and Prevention*, "Smoking and Cancer," April 2, 2021, available at https://www.cdc.gov/tobacco/campaign/tips/diseases/cancer.html.

122 *National Toxicology Program, Department of Health and Human Services*, "15th Report on Carcinogens," December 21, 2021, available at https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/roc/index.html.

123 *National Toxicology Program, Department of Health and Human Services*, "Substances Listed in the Fifteenth Report on Carcinogens," Dec 21, 2021, available at https://ntp.niehs.nih.gov/ntp/roc/content/listed_substances_508.pdf.

124 *Centers for Disease Control and Prevention*, "Current Cigarette Smoking Among Adults in the United States," December 10, 2020, available at https://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/index.htm. *See also*, Whitmer, Michelle, "Asbestos Facts & Statistics," *Asbestos.com*, August 20, 2021, available at https://www.asbestos.com/asbestos/statistics-facts/.

occurring exposures (e.g., ultraviolet light, radon gas, infectious agents), medical treatments (e.g., radiation and medicines including chemotherapy, hormone drugs, drugs that suppress the immune system), workplace exposures, household exposures, and pollution.[125]

84. As advised by the National Cancer Institute, "many factors influence whether a person exposed to a carcinogen will develop cancer, including the amount and duration of the exposure and the individual's genetic background."[126] Some carcinogens are carcinogenic if a person is exposed in a specific way (e.g., swallowing as opposed to touching it).[127] Consider the following examples:

- Asbestos -- Low levels of asbestos are present in the air, water and soil; most people are exposed to asbestos at some point during their lifetime. People who become sick from asbestos are typically those who are exposed to it on a regular basis (e.g., people who work directly with the material). How asbestos exposure affects an individual depends on many factors including: dose, duration, size/shape/chemical makeup of the asbestos fibers, source of exposure, individual risk factors (e.g., smoking), and genetic factors (e.g., having a germline mutation).[128]
- Smoking -- The National Cancer Institute estimated that people who consistently smoked an average of less than one cigarette per day over their lifetime had a 64 percent higher risk of earlier death than never smokers and nine times the risk of dying from lung cancer. Those who smoked between one and 10 cigarettes a day had

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125 *American Cancer Society*, "Determining if Something Is a Carcinogen," May 17, 2019, available at https://www.cancer.org/cancer/cancer-causes/general-info/determining-if-something-is-a-carcinogen.html.

126 *National Cancer Institute*, "Cancer-Causing Substances in the Environment," December 28, 2018, available at https://www.cancer.gov/about-cancer/causes-prevention/risk/substances.

127 *American Cancer Society*, "Known and Probable Human Carcinogens," available at https://www.cancer.org/cancer/cancer-causes/general-info/known-and-probable-human-carcinogens.html. *See also*, *American Cancer Society*, "Determining if Something Is a Carcinogen," May 17, 2019, available at https://www.cancer.org/cancer/cancer-causes/general-info/determining-if-something-is-a-carcinogen.html.

128 *National Cancer Institute*, "Asbestos Exposure and Cancer Risk," November 19, 2021, available at https://www.cancer.gov/about-cancer/causes-prevention/risk/substances/asbestos/asbestos-fact-sheet#who-is-at-risk-for-an-asbestos-related-disease.

an 87 percent higher risk of earlier death than never smokers, and almost twelve times the risk of dying from lung cancer.[129]

85. Even if a substance or exposure is known or suspected to cause cancer, the benefits of a substance or exposure can outweigh the risks. For example, X-ray imaging exams are a valuable medical tool for an array of examinations and procedures.[130] Small doses of gamma and X-radiation, however, increase cancer risk by a small amount; for example, the FDA estimates that exposure to 10 mSv from an imaging test would increase the risk of death from cancer by about 1 in 2,000 patients.[131] A CT scan of the abdomen and pelvis, for example, exposes a patient to about 10 mSv.[132] The increase in the risk of death from cancer associated with this single imaging test is larger than the incremental risk from taking either the highest possible exposure to NDMA or the highest possible exposure to NDEA through affected valsartan. Yet there is no such screening guideline that suggests people who have had one or multiple CT scans in the past should be subject to further screening than the general asymptomatic population, who are recommended not to undergo screening. Within radiation from imaging tests alone, patients can be exposed to a wide variation in incremental risk, based on the type, number, and frequency of imaging tests that they receive during their care.

86. Professor Song does not account for proposed class members' exposure to potential carcinogens in his class-wide methodology. Underlying exposure needs to be accounted for in order to determine the appropriate patient clinical care. This requires an individualized review of each patient. Take as examples two of the named medical monitoring proposed class members for illustration, both of whom present individualized risk factors that would stand far

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129 *National Cancer Institute*, "No Safe Level of Smoking: Even low-intensity smokers are at increased risk of earlier death,", December 5, 2016, available at https://www.cancer.gov/news-events/press-releases/2016/low-intensity-smoking-risk.

130 *U.S. Food and Drug Administration*, "Medical X-ray Imaging," September 28, 2020, available at https://www.fda.gov/radiation-emitting-products/medical-imaging/medical-x-ray-imaging.

131 *American Cancer Society*, "Do X-rays and Gamma Rays Cause Cancer?" available at https://www.cancer.org/cancer/cancer-causes/radiation-exposure/x-rays-gamma-rays/do-xrays-and-gamma-rays-cause-cancer.html.

132 *American Cancer Society*, "Understanding Radiation Risk from Imaging Tests," available at https://www.cancer.org/treatment/understanding-your-diagnosis/tests/understanding-radiation-risk-from-imaging-tests.html.

ahead of NDMA and NDEA exposure in any healthcare provider's consideration of an appropriate cancer screening plan for each individual:

- [redacted][133][redacted][134][redacted].[135][redacted].[136][redacted].[137][redacted][138][redacted]

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133 Deposition of Michael Rives, May 26, 2021 ("Rives Deposition"), Exhibit MR0001, pp. 2–4.

134 Rives Deposition, 31:17–32:25, 33:1–13, 43:5–23, 44:10–23.

135 *Centers for Disease Control and Prevention*, "Mining Topic: Respiratory Diseases," September 3, 2021, available at https://www.cdc.gov/niosh/mining/topics/respiratorydiseases.html. *See also*, *Dana-Farber Cancer Institute*, "Which Professions are Associated with Cancer Risk?," August 3, 2019, available at https://blog.dana-farber.org/insight/2019/08/which-professions-are-associated-with-cancer-risk/.

136 Rives Deposition, 29:7–11, 149:17–22. *See also*, *U.S. Department of Veterans Affairs*, "Agent Orange exposure and VA disability compensation," available at https://www.va.gov/disability/eligibility/hazardous-materials-exposure/agent-orange/.

137 Diseases include AL amyloidosis, bladder cancer, chronic B-cell leukemias, chloracne, diabetes mellitus type 2, Hodgkin's disease, hypothyroidism, ischemic heart disease, multiple myeloma, non-Hodgkin's lymphoma, parkinsonism, Parkinson's disease, porphyria cutanea tarda, prostate cancer, respiratory cancers (including lung cancer), and soft tissue sarcomas. *See, e.g.*, *U.S. Department of Veterans Affairs*, "Veterans' Diseases Associated with Agent Orange," available at https://www.publichealth.va.gov/exposures/agentorange/conditions/.

138 Rives Deposition, Exhibit MR0001, p.22.

[redacted]139

- [redacted]140 [redacted]141 [redacted]142

87. Determining which proposed class members were exposed to other known carcinogens that pose a far greater risk of cancer than NDMA and NDEA, and therefore would influence a healthcare provider's assessment of which specific cancer screenings to potentially recommend, would require individualized review.

C. Exposure to NDMA and NDEA varies by patient

88. Even assuming exposure to NDMA and NDEA was a relevant consideration in cancer screening decisions, such exposure is itself highly variable and cannot be reduced to a single source such as affected valsartan. As described above in **Section III.B**, the FDA estimated a small incremental cancer risk associated with use of valsartan with NDMA and NDEA impurity. Specifically, the FDA estimated that at the highest dose of valsartan, one additional cancer case may be expected per 8,000 patients exposed to NDMA-containing valsartan and one additional cancer case may be expected per 18,000 patients exposed to NDEA-containing valsartan.[143] The former estimate is comparable to the lifetime odds of death from sunstroke

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139 *National Cancer Institute*, "No Safe Level of Smoking: Even low-intensity smokers are at increased risk of earlier death,", December 5, 2016, available at https://www.cancer.gov/news-events/press-releases/2016/low-intensity-smoking-risk.

140 Deposition of Valerie Rodich-Annese, March 9, 2021 ("Rodich-Annese Deposition"), Exhibit VA0001, pp. 2–3, 36.

141 Rodich-Annese Deposition, Exhibit VA0001, p. 22.

142 *National Cancer Institute*, "No Safe Level of Smoking: Even low-intensity smokers are at increased risk of earlier death," December 5, 2016, available at https://www.cancer.gov/news-events/press-releases/2016/low-intensity-smoking-risk.

143 *U.S. Food & Drug Administration*, "Laboratory analysis of valsartan products," May 2, 2019, available at https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products.

(1 in 8,248) or from an accidental gun discharge (1 in 8,571) and both estimates are far below lifetime odds of death from other causes, such as a motor vehicle crash (1 in 107) or drowning (1 in 1,128).[144] As discussed above, there is reason to believe the FDA's estimates may overstate the incremental cancer risk from affected valsartan use given two studies found that exposure to affected valsartan was not associated with a significantly elevated risk of developing cancer overall.[145] In addition, the FDA's estimates are based on the assumption that all patients took the highest valsartan dose of 320mg and that those 320mg tablets contained the highest levels of NDMA and NDEA impurity.[146] In reality, the incremental cancer risk will vary considerably across patients who consumed affected valsartan due to variability in valsartan dosage and duration of therapy, variability in NDMA and NDEA impurity across valsartan manufacturers, and variability across lots within valsartan manufacturers. This variability is further described and demonstrated in **Figure 6** below.

89. The specific dose a patient takes of a valsartan will depend on the indication (i.e., the condition the valsartan is being used to treat) and patient characteristics, such as age, comorbidities, and response to the medication. For example, typical doses of valsartan for high blood pressure are 80mg and 160mg once daily, and a common dose for heart failure is 40mg twice per day.[147] Doses are even lower for valsartan used for left ventricular failure after a heart attack (20mg twice a day).[148] Adult doses may be titrated upwards for each indication, but typically do not exceed 320 mg per day.[149] Some patients with hypertension may respond with acceptable blood pressures to valsartan at lower doses, while others may require higher doses. Many clinicians

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144 *National Safety Council Injury Facts*, "Odds of Dying," available at https://injuryfacts.nsc.org/all-injuries/preventable-death-overview/odds-of-dying/.

145 See footnote 30.

146 Johnson, George E., *et al.,* "Permitted daily exposure limits for noteworthy N-nitrosamines," *Environmental and Molecular Mutagenesis*, May 2021, pp. 293–305 at p. 294 ("The values obtained indicated a theoretical excess lifetime cancer risk of 1 in 8000, assuming consumption of the highest prescribed dose of valsartan (320 mg/day), with the highest levels of NDMA, for 4 years (FDA, 2018).").

147 *Mayo Clinic*, "Valsartan (Oral Route)," July 1, 2021, available at https://www.mayoclinic.org/drugs-supplements/valsartan-oral-route/proper-use/drg-20067355.

148 *Mayo Clinic*, "Valsartan (Oral Route)," July 1, 2021, available at https://www.mayoclinic.org/drugs-supplements/valsartan-oral-route/proper-use/drg-20067355.

149 *Mayo Clinic*, "Valsartan (Oral Route)," July 1, 2021, available at https://www.mayoclinic.org/drugs-supplements/valsartan-oral-route/proper-use/drg-20067355.

may prescribe additional agents to lower blood pressure, rather than increase the dose of valsartan to its maximum.[150]

90. Total alleged exposure to NDMA and NDEA from affected valsartan will vary based on the dosage and the duration of therapy. Based on an analysis of the OptumHealth data, I find that patients took a range of dosage strengths of affected valsartan,[151] and their duration of therapy with this drug ranged from less than a month to nearly 51 months (I do not evaluate use longer than 51 months due to data availability). Specifically, more than 40 percent of patients took affected valsartan for less than three months and 66 percent took affected valsartan for less than a year.[152] While an individualized analysis relying on complete patient data on valsartan use over the at-issue period would be necessary to determine which patients meet Plaintiffs' definition of the Lifetime Cumulative Threshold of intake of NDMA and NDEA for inclusion in the proposed class, the results highlight the fact that alleged exposure would vary substantially across patients.[153] Even those patients that would meet the proposed class definition can vary substantially in terms of alleged exposure to NDMA and NDEA since they can consume affected valsartan at different doses and for different lengths of time. Furthermore, many such proposed class members would have far lower alleged NDMA and NDEA exposure than studied by the FDA when evaluating cancer risk. For example, the Medical Monitoring Complaint claims that patients taking a 320 mg dose valsartan where the active ingredient is produced by ZHP for three months may be eligible for the class.[154] It is

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[150] Kalra, Sanjay, *et al.*, "Combination therapy in hypertension: An update," *Diabetology & Metabolic Syndrom*e, 2010.

[151] *See* a summary of the number of patients and prescriptions for each dosage of affected valsartan in my backup materials.

[152] The calculations of the percentages of patients taking affected valsartan (see footnote 23) and their duration of treatment are based on claims in the OptumHealth data for 15,258 patients that had at least one prescription of affected valsartan from January 2012 (beginning of the at-issue period) through March 2017 (end of data availability). These patients also had continuous eligibility from three months prior to their first affected valsartan prescription through three months after their last affected valsartan prescription. The duration of treatment was calculated as the number of months from the date of the first affected valsartan prescription through the end of the last affected valsartan prescription observed in the OptumHealth data (including the days of supply associated with the last affected valsartan prescription).

[153] Medical Monitoring Complaint, ¶¶538–541.

[154] Medical Monitoring Complaint, ¶541.

also evident from my OptumHealth analysis that many patients taking affected valsartan for at least three months may stop taking affected valsartan within a year. Such limited treatment duration falls well below the four years that the FDA considers when evaluating the potential for cancer risk related to the *highest* daily dose of valsartan treatments (320 mg).[155]

91. Moreover, the FDA explicitly advised patients taking affected valsartan to continue taking it until a safe alternative was prescribed, highlighting the important health benefits of valsartan as a maintenance therapy.[156] Thus, some patients may have continued therapy with affected valsartan beyond recall announcements. However, patients may have discontinued valsartan and switched to an alternative therapy during the at-issue period due to other reasons, including contraindications, adverse events, or side effects. For example, the label indicates valsartan should be discontinued when pregnant and enumerates several adverse reactions, including hypotension and increased blood creatinine, that patients may experience on therapy.[157] Other common side effects of valsartan may be idiosyncratic and patient-specific, including nausea, cough, dizziness, fatigue, diarrhea, headache, and abdominal pain.[158] In valsartan clinical trials, between 2% and 10% of patients discontinued therapy as a result of an adverse reaction or side effect, depending on the therapeutic indication.[159]

92. High variability in the amount of nitrosamine present in a given valsartan creates further variability in patients' exposure to NDMA and NDEA, and in turn, patients' potential incremental cancer risk, if any, attributable to affected valsartan. According to an FDA laboratory analysis, nitrosamine levels in valsartan tablets varied both between manufacturers

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155 *U.S. Food & Drug Administration*, "Laboratory analysis of valsartan products," May 2, 2019, available at https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products.

156 *U.S. Food & Drug Administration*, "Recalls of Angiotensin II Receptor Blockers (ARBs) including Valsartan, Losartan and Irbesartan," February 3, 2021, available at https://www.fda.gov/drugs/drug-safety-and-availability/recalls-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and-irbesartan.

157 *U.S. Food & Drug Administration*, "Highlights of Prescribing Information, Diovan (valsartan) Tablets," available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021283s033lbl.pdf.

158 *RxList*, "Diovan," April 28, 2021, available at https://www.rxlist.com/diovan-drug.htm#side_effects.

159 *RxList*, "Diovan," April 28, 2021, available at https://www.rxlist.com/diovan-drug.htm#side_effects.

and across lots within manufacturers.[160] When above detectable levels, average levels of NDMA ranged from 0.33 to 20.19 µg per 320 mg and levels of NDEA ranged from 0.02 to 2.62 µg per 320 mg.[161] As noted in **Section III.B** of this report, the FDA has specified acceptable intake levels of 0.096 µg/day for NDMA and 0.0265 µg/day for NDEA, which correspond to approximately 2,454 µg and 678 µg in cumulative lifetime exposure, respectively.[162] According to the minimum and maximum *detected* levels from the FDA's analysis, a patient on a daily 320 mg valsartan regimen for four years would be exposed to anywhere from 482 to 29,498 µg of NDMA and 29 to 3,828 µg of NDEA.[163] While these ranges include the FDA's acceptable levels of cumulative lifetime exposure, I have previously noted that the FDA's acceptable intake levels may be conservatively low *and* several lots of valsartan analyzed by the FDA included levels of NDMA and NDEA that were below the limit of detection (effectively bounding the bottom of the ranges by 0).[164]

93. The FDA's estimates of incremental cancer risk are based on simple linear extrapolations, not health outcome data like the two European studies discussed above. Consider the lifetime acceptable intake of NDMA of 2,454 µg, which corresponds to a 1 in 100,000 excess cancer risk. The maximum exposure to NDMA from affected valsartan of 29,498 µg is approximately 12 times the lifetime acceptable intake, implying an excess cancer risk of 12 in 100,000 or

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160 *U.S. Food & Drug Administration*, "Laboratory analysis of valsartan products," May 2, 2019, available at https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products.

161 *U.S. Food & Drug Administration*, "Laboratory analysis of valsartan products," May 2, 2019, available at https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products.

162 Calculated over 70 years; see backup materials. *U.S. Food & Drug Administration*, "FDA Updates and Press Announcements on Angiotensin II Receptor Blocker (ARB) Recalls (Valsartan, Losartan, and Irbesartan): FDA updates table of interim limits for nitrosamine impurities in ARBs," February 28, 2019, available at https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan#interimlimits2.

163 The minimum and maximum detectable levels per 320mg were 0.33 µg and 20.19 µg for NDMA and 0.02 µg and 2.62 µg for NDEA (the latter level is from 1.31 µg observed in a 160mg tablet); see backup materials for supporting calculations. The maximum detectable level for NDEA is based on 1.31 µg detected in a 160mg tablet. *U.S. Food & Drug Administration*, "Laboratory analysis of valsartan products," May 2, 2019, available at https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products.

164 Johnson, George E., *et al.,* "Permitted daily exposure limits for noteworthy N-nitrosamines," *Environmental and Molecular Mutagenesis*, May 2021, pp. 293–305. *See also*, *U.S. Food & Drug Administration*, "Laboratory analysis of valsartan products," May 2, 2019, available at https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products.

approximately 1 in 8,000. **Figure 6** below reproduces these calculations for *all* detected levels of NDMA and NDEA in the FDA's analysis, following their assumption of a 320 mg daily dose for four years. The table additionally includes estimates of the incremental cancer risk associated with hypothetical average exposure levels for each nitrosamine. The outlined incremental cancer risks correspond to those reported by the FDA (unrounded). However, it is evident from the table that actual risks may very well be much lower. Using the unweighted average nitrosamine levels, for example, the incremental cancer risk is only 1 in approximately 43,000 for NDMA and 1 in approximately 160,000 for NDEA. Note that these estimates still assume a 320 mg daily dose over 4 years. Lower dosages and/or durations of therapy will therefore translate to even lower cancer risk. In fact, the FDA specifically states: "Notably, we would like to stress that the actual risk to patients is likely much lower than our estimates, which reflect a scientific assessment of the highest possible exposure."[165]

[165] *U.S. Food & Drug Administration*, "Statement on the Agency's Ongoing Efforts to Resolve Safety Issue with ARB Medications," August 28, 2019, available at https://www.fda.gov/news-events/press-announcements/statement-agencys-ongoing-efforts-resolve-safety-issue-arb-medications.

Figure 6. Incremental cancer risk by nitrosamine level in affected valsartan products

Company	Product (tablets)	Total Lots Tested	Nitrosamine Level (µg per 320mg)		Incremental Cancer Risk (individuals per +1 cancer case)	
			NDMA	NDEA	NDMA	NDEA
Aurobindo	AML 10mg/VLS 320 mg	3	Below LOD	0.02-0.09	N/A	515,278 - 2,318,750
Aurobindo	VLS 320mg	3	Below LOD	0-0.05	N/A	927,500*
Aurobindo	VLS 320mg/HCT 25mg	3	Below LOD	0.02-0.19	N/A	244,079 - 2,318,750
Hetero Labs	VLS 320mg	3	0.33-0.44	Below LOD	381,818 - 509,091	N/A
Mylan	AML 10mg/VLS 320 mg	3	Below LOD	0.04-0.11	N/A	421,591 - 1,159,375
Mylan	AML 10mg/VLS 320 mg/HCT 25mg	1	Below LOD	0.05	N/A	927,500
Mylan	VLS 320mg	3	Below LOD	0.07-0.16	N/A	289,844 - 662,500
Mylan	VLS 320mg/HCT 25mg	3	Below LOD	0.20-0.38	N/A	122,039 - 231,875
Prinston	VLS 320mg	3	15.18-16.30	Below LOD	10,307 - 11,067	N/A
Prinston	VLS 320mg/HCTZ 25mg	3	13.18-20.19	Below LOD	8,321 - 12,747	N/A
Teva	AML 10mg/VLS 320 mg	6	Below LOD	0-0.03	N/A	1,545,833*
Teva	AML 10mg/VLS 320 mg/HCT 25mg	5	Below LOD	0-0.03	N/A	1,545,833*
Teva	VLS 320mg	2	7.92-16.55	Below LOD	10,151 - 21,212	N/A
Teva	VLS 320mg/HCTZ 25mg	3	6.94-10.35	0-0.77	16,232 - 24,207	60,227*
Torrent	AML 10mg/VLS 320 mg/HCTZ 25mg	3	10.24-11.53	Below LOD	14,571 - 16,406	N/A
Torrent	VLS 320mg	2	0.56-0.62	1.12-1.22	270,968 - 300,000	38,012 - 41,406
Torrent	VLS 160mg	1	0.90	2.62	186,667	17,700
	Product average					
	Unweighted		3.886	0.289	43,230	160,239
	Lot-weighted		3.671	0.167	45,759	278,529

Notes:

[1] AML = amlodipine; HCT/HCTZ = hydrochlorothiazide; LOD = limit of detection; VLS = valsartan

[2] Nitrosamine level of zero is assumed for lots with levels below the limit of detection

[3] Nitrosamine levels for 160mg products converted from µg per tablet (in source) to µg per 320mg by multiplying by two

[4] Averages are calculated using the midpoint of the reported range for each product

[5] Lower limits of nitrosamine levels correspond to upper limits of incremental cancer risk

[6] For products where the detected range of NDMA or NDEA includes zero, the incremental risk reflects the upper limit of the range only (*)

Source: *U.S. Food & Drug Administration*, "Laboratory analysis of valsartan products," May 2, 2019, available at https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products.

94. Dietary choices alone may bring cumulative lifetime exposure to NDMA or NDEA within these ranges or above the FDA's acceptable levels, irrespective of pharmacologic treatment. Consider the case of bacon, a breakfast staple regularly consumed by a majority of Americans,[166] for which NDMA levels range from 0.67-3.92 µg/kg.[167] As shown in **Figure 7**, these levels correspond to 0.02 to 0.09 µg for a serving of two slices. For an individual who consumes 5 pounds of bacon annually,[168] detected levels imply between 76 µg and 445 µg of NDMA exposure over 50 years from bacon alone.[169] Over 70 years, the exposure range becomes 106 µg to 622 µg, which is below the FDA cumulative lifetime exposure limit of 2,454 µg for NDMA. Exposure levels may be substantially higher for skillet-fried bacon with especially high fat content or substantially lower for bacon cooked in a microwave.[170] Beer has also been shown to contain potentially high levels of NDMA per kg (0-1.87 µg/kg).[171] One 16-oz pint of beer therefore contains up to 0.889 µg of NDMA (**Figure 7**). According to a Gallup poll, the United States consumed 26.2 gallons per drinking age adult in 2018 (equivalent to about 4 pints per person per week).[172] Under the assumption that 1 gallon of beer weighs 8 pounds or 3.63 kg, the average drinking age adult was therefore exposed to up to 178 µg of NDMA in 2018 alone. Extrapolating over 50 years, exposure may be as high as 8,892 µg.

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166 *Statista*, "U.S. population: Do you eat bacon?" 2021, available at https://www.statista.com/statistics/279771/us-households-consumption-of-bacon/.

167 Park, Jong-eun, *et al.,* "Distribution of seven N-nitrosamines in food," *Toxicological Research,* Vol. 31, No. 3, September 30, 2015, pp. 279–288.

168 Approximately 10 to 20 million Americans consumed 5 or more pounds of bacon in each year from 2011 to 2020. *Statista*, "U.S. population: Amount of bacon consumed from 2011 to 2020," 2021, available at https://www.statista.com/statistics/282269/us-households-amounts-of-bacon-consumed-trend/.

169 See backup materials for calculations in this paragraph.

170 Miller, B. J., *et al.,* "Formation of N-nitrosamines in Microwaved versus Skillet-Fried Bacon Containing Nitrite," *Food and Chemical Toxicology*, 1989, Vol. 27, No. 5, pp. 295–299.

171 Park, Jong-eun, *et al.,* "Distribution of seven N-nitrosamines in food," *Toxicological Research,* Vol. 31, No. 3, September 30, 2015, pp. 279–288.

172 Stebbins, Samuel, "How much beer does your state drink? In the thirstiest, about 40 gallons a year per person," *USA Today*, September 14, 2019, available at https://www.usatoday.com/story/money/2019/09/14/how-much-beer-did-the-average-person-drink-in-every-state/40109241/.

Figure 7. NDMA and NDEA levels in common foods and beverages

Food/Beverage	Serving (amount)	Weight (kg)	NDMA		NDEA	
			Range of detected levels (µg/kg)	Exposure per serving (µg)	Range of detected levels (µg/kg)	Exposure per serving (µg)
Fresh vegetables	1 cup	0.076	ND - 6.01	Up to 0.457	ND - 1.53	Up to 0.116
Fish	1 fillet	0.176	0.04 - 3.5	0.007 - 0.616	0.06 - 4.2	0.011 - 0.739
Chicken	1 piece	0.174	ND - 0.52	Up to 0.09	ND	N/A
Bacon	2 slices	0.023	0.67 - 3.92	0.015 - 0.09	0.17 - 0.77	0.004 - 0.018
Cheese	1 slice	0.017	ND - 3.0	Up to 0.051	ND - 4.0	Up to 0.068
Pasta	1/2 cup	0.056	ND - 0.72	Up to 0.04	ND - 2.81	Up to 0.157
Margarine	1 tablespoon	0.014	0.2 - 5.8	0.003 - 0.081	1.4 - 5.5	0.02 - 0.077
Olive oil	1 tablespoon	0.013	0.98 - 3.5	0.013 - 0.047	1.7 - 3.6	0.023 - 0.048
Beer	1 pint	0.475	ND - 1.87	Up to 0.889	ND - 1.14	Up to 0.542

Notes:

[1] One study excluded from olive oil ranges because only average levels were reported

[2] NDMA and NDEA levels associated with pasta correspond to those reported for "Noodle" in source

[3] Average servings in ounces converted to kilograms by multiplying by 0.028

[4] ND = not detected

Sources:

[1] Park, Jong-eun, et al., "Distribution of seven N-nitrosamines in food," *Toxicological Research*, Vol. 31, No. 3, September 30, 2015, pp. 279-288.

[2] *U.S. Department of Agriculture*, "FoodData Central," available at: https://fdc.nal.usda.gov/fdc-app.html.

[3] *Wegmans Food Markets*, Product Search, available at https://www.wegmans.com/.

95. Nitrosamines have also been found in numerous personal care products.[173] Among specific nitrosamines, the highest concentrations have been observed for NDELA (N-nitrosodiethanolamine) and NMOR (N-nitrosomorpholine), both considered "possibly carcinogenic to humans" by the International Agency for Research on Cancer ("IARC").[174] However, levels of more potent NDMA and NDEA—considered "probably carcinogenic to

[173] Gushgari, Adam J., and Rolf U. Halden, "Critical review of major sources of human exposure to N-nitrosamines," *Chemosphere,* Vol. 210, 2018, pp. 1124–1136.

[174] Gushgari, Adam J., and Rolf U. Halden. "Critical review of major sources of human exposure to N-nitrosamines," *Chemosphere*, Vol. 210, 2018, pp. 1124–1136, at pp. 1126, 1128. *See also*, *International Agency for Research on Cancer*, "Agents classified by the IARC Monographs, Volumes 1-130," November 30, 2021, available at https://monographs.iarc.who.int/agents-classified-by-the-iarc/.

humans" by the IARC—have been detected as well.[175] For example, a recent study detected levels of NDEA in 9 different personal care products, with average concentrations ranging from 1.76 µg/kg (skin toner) to 11.24 µg/kg (hand cream).[176] Concentrations of NDEA observed for shampoo, shower gel, and conditioner were comparable to concentrations of NDMA reported in an earlier study that only analyzed NDMA, NMOR and NDELA.[177]

96. Finally, as noted previously, humans are also exposed to nitrosamines through endogenous sources. Because nitrosamines are formed by the reaction of nitrite with secondary amines, they can form endogenously in the human body when the reaction occurs internally. Nitrites may be ingested directly from certain foods or formed from nitrates, which are ingested and then reduced to nitrites by bacteria in the mouth or enzymes in the body. Nitrites are often added to processed meats as preservatives and flavor enhancers, while nitrates are naturally found in leafy vegetables (e.g., spinach) and root vegetables (e.g., beets).[178] Amines are also present in the body from ingested foods and are commonly found in fermented food products.[179] Like external exposure, endogenous exposure to nitrosamines will vary across people depending on dietary levels of these nitrosamine precursors (i.e., nitrite, nitrate, amines)

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[175] Spiegelhalder, B., and R. Preussmann, "Contamination of toiletries and cosmetic products with volatile and nonvolatile N-nitroso carcinogens," *Journal of Cancer Research and Clinical Oncology*, Vol. 108, No. 1, 1984, pp. 160–163 at p. 162. *See also*, Lim, Duck Soo, *et. al.*, "Risk assessment of N-nitrosodiethylamine (NDEA) and N-nitrosodiethanolamine (NDELA) in cosmetics," *Journal of Toxicology and Environmental Health, Part A*, Vol. 81, No. 12, 2018, pp. 465–480; *International Agency for Research on Cancer*, "Agents classified by the IARC Monographs, Volumes 1-130," November 30, 2021, available at https://monographs.iarc.who.int/agents-classified-by-the-iarc/.

[176] The nine products were shampoo, cleansing foam, shower gel, hair styling product, hand cream, eye cream, face cream, skin toner, and hair conditioner. Lim, Duck Soo, *et. al.*, "Risk assessment of N-nitrosodiethylamine (NDEA) and N-nitrosodiethanolamine (NDELA) in cosmetics," *Journal of Toxicology and Environmental Health, Part A,* Vol. 81, No. 12, 2018, pp. 465–480 at p. 468.

[177] Spiegelhalder, B., and R. Preussmann, "Contamination of toiletries and cosmetic products with volatile and nonvolatile N-nitroso carcinogens," *Journal of Cancer Research and Clinical Oncology*, Vol. 108, No. 1, 1984, pp. 160–163 at p. 161. *See also*, Lim, Duck Soo, *et. al.*, "Risk assessment of N-nitrosodiethylamine (NDEA) and N-nitrosodiethanolamine (NDELA) in cosmetics," *Journal of Toxicology and Environmental Health, Part A*, Vol. 81, No. 12, 2018, pp. 465–480 at p. 468.

[178] Keller, Rosa M., *et al.*, "Dietary Nitrate and Nitrite Concentrations in Food Patterns and Dietary Supplements," *Nutrition Today*, Vol. 55, No. 5, 2020, pp. 218–226.

[179] Doeun, Dara, *et al.*, "Biogenic amines in foods," *Food Science and Biotechnology*, Vol. 26, No. 6, 2017, pp. 1463–1474.

and physiological characteristics (e.g., pH, levels of nitrosating bacteria).[180] Additionally, there is evidence that endogenous exposure is the primary source of nitrosamine exposure in humans and a stronger predictor of cancer risk than external exposure.[181]

97. As discussed, exposure to NDMA and NDEA can arise from a range of sources and varies substantially across individuals. Even if exposure to NDMA and NDEA or carcinogens more broadly was a consideration in a cancer screening recommendation, exposure is not limited to the use of affected valsartan. Professor Song fails to acknowledge the individualized nature of cancer screening, which is typically determined on a patient-by-patient basis by a provider, depending on patients' characteristics, lifestyle risk factors, overall health condition, and hereditary traits/risks among other factors. Instead, Professor Song casts a wide net by suggesting that all proposed class members will be subject to the six medical monitoring services that he identified in Table 6 of this report. Many individual patient factors are far more important than exposure to carcinogens, specifically the use of affected valsartan, in determining an individualized recommendation for cancer screening. Individualized inquiry would be necessary to determine if cancer screening would be appropriate for any proposed class member; it would be unlikely that a patient's use of affected valsartan has a meaningful impact on that decision relative to the numerous other factors considered in determining a screening recommendation.

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[180] Fristachi, Anthony, and Glenn Rice, "Estimation of the total daily oral intake of NDMA attributable to drinking water," *Journal of Water and Health*, Vol. 5, No. 3, 2007, pp. 341–355 at p. 343.

[181] Fristachi, Anthony, and Glenn Rice, "Estimation of the total daily oral intake of NDMA attributable to drinking water," *Journal of Water and Health*, Vol. 5, No. 3, 2007, pp. 341–355 at p. 348. *See also*, Tricker, A.R., "N-nitroso compounds and man: sources of exposure, endogenous formation and occurrence in body fluids," *European Journal of Cancer Prevention*, Vol. 6, No. 3, 1997, pp. 226–268. (See footnote 36 for more details); Jakszyn, Paula, *et al.*, "Endogenous versus exogenous exposure to N-nitroso compounds and gastric cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST) study," *Carcinogenesis*, Vol. 27, No. 7, 2006, pp. 1497–1501.

VI. PROFESSOR SONG'S ANALYSIS FAILS TO CONSIDER THE TRUE EXTENT OF VARIABILITY IN SERVICES AND COSTS IN THE PROPOSED MEDICAL MONITORING CLASS

98. The impracticality of the screening assumptions underlying Professor Song's opinions highlight a central flaw in his methodology. Professor Song's "common methodology" of estimating medical monitoring spending has little relevance to the actual costs, services, and medical monitoring needs of individual members of the proposed class. Without an ability to determine the medical monitoring needs of each proposed class member and identify the costs of these services for each patient, Professor Song's "common methodology" is fundamentally flawed.

99. Professor Song acknowledges that estimating spending for a monitoring program would necessitate an estimation of the "size and composition of the patient population undergoing monitoring."[182] Yet Professor Song himself makes no effort to identify the "size and composition" of the proposed class to identify the relevant monitoring program, which is, in any event, an individualized consideration and not a class-wide consideration. Moreover, according to Professor Song, the costs of monitoring for each patient will vary substantially due to variation in a number of key factors, including "the insurer mix, site of care composition, and network status of the providers for the patient population."[183] However, Professor Song ignores this variation in his estimation and simply assumes that all proposed class members would receive the same medical monitoring tests and procedures, and that prices of those tests and procedures would reflect the broad average of Medicaid, Medicare, and commercial insurer prices. Not only are these broad average prices speculative, but Professor Song provides no reason to believe that the prices paid by the types of patients that comprise the proposed class members are consistent with the overall national average prices that he references. Furthermore, even among the proposed class members, the types of monitoring services indicated and the prices associated with those services will vary substantially.

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[182] Song Report, ¶39.

[183] Song Report, ¶39.

100. The variation in each of these individual considerations is likely to be correlated in complicated ways across considerations (i.e., each consideration is not statistically independent from one another). As a result, any effort to estimate the aggregate cost of monitoring would require collecting individualized data on every proposed class member on whether they would be indicated for monitoring in the absence of the use of affected valsartan, whether they would be indicated for monitoring in the presence of the use of affected valsartan, and details of their insurance arrangement. Within each of these categories, there would be a multitude of questions to consider that are most appropriately addressed between each patient and their physicians.

101. Furthermore, Professor Song cites total price estimates for his selected medical monitoring services but fails to account for the fact that the proposed class members will pay only a small share (if any) of the total price. Patients with insurance do not pay the full cost of cancer tests and screening procedures. Rather patients may pay a share of the costs that reflect the specific cost-sharing arrangements for that patient's insurance coverage (as well as the patient's overall health care spending to date if the patient is responsible for some level of deductible). Determining the share of costs that any individual proposed class member would pay today or in the future would require individualized inquiry.

102. Finally, Professor Song notes that "projecting future health care use requires assumptions about life expectancy and the development of medical conditions (e.g., cancer and other acute and chronic diseases) that may render the monitoring program *less appropriate clinically*,"[184] (emphasis added) which clearly suggests the need for individualized inquiry. Equally problematic is the fact that future prices for the services that comprise any medical monitoring program are largely unknown. It would be challenging to identify current prices for proposed class members given their existing insurance choices. Insurance plan composition will change over time as patients transition to Medicare, patients transition in and out of Medicaid insurance, uninsured individuals qualify for insurance coverage, and patients change private commercial insurance carriers. Furthermore, the prices of medical monitoring services covered

[184] Song Report, ¶39.

by different insurers will evolve in ways that are challenging to predict and will vary for different types of insurers. These challenges are further complicated by the fact that Professor Song does not consider the time frame over which the medical monitoring services will be provided and how far into the future it would be necessary to anticipate the myriad changes in costs.

103. In this section, I outline three factors that can cause healthcare spending to vary currently. The variability within each factor is extensive, and the variability is just compounded when all three factors are layered. Lastly, I outline that the interaction of these factors is further complicated in the future. In the future, there may be technology changes that improve screening processes and/or treatment options, which may influence the benefit-harm trade-offs providers consider when deciding whether and what screening is appropriate for a given individual patient.

A. Variation in prices

104. Professor Song acknowledges that the current price of a healthcare service differs both *between* and *within* insurers, depending on whether the patients are insured by commercial, Medicare, or Medicaid insurance, the location and type of facility providing the service, and whether the provider is in or out of network.[185] All these factors yet again highlight the need for individualized inquiry.

105. Professor Song assumes the foundation of the potential monitoring program could begin with "a urinalysis on an annual basis, a complete blood count on an annual basis, an evaluation and management (office visit) on an annual basis, a low-dose computed tomography ("CT") chest imaging test on an annual basis, an upper endoscopy every five years, and a screening colonoscopy every five years."[186] Professor Song's Table 6 provides Medicare prices and estimated Medicaid and commercial prices for those services delivered in a freestanding physician office in 2021. Even accepting Professor Song's assumptions of the testing involved in a baseline medical monitoring program, which, for the reasons discussed above, must itself

[185] Song Report, ¶31.

[186] Song Report, ¶32.

vary by patient in accordance with individualized factors, this table masks significant variation that needs to be accounted for.

106. While Medicare prices for a specific test or procedure are calculated based on a standard methodology involving "Relative Value Unit" calculations, the resulting prices can vary across providers in different geographic locations, and the patient screening costs can vary both as a result of the price variation for specific services as well as variation in the services provided to any individual patient. Relative Value Units ("RVUs") are the foundation of the Medicare Physician Fee Schedule and the basis of most commercial fee schedules.[187] As explained in the Song Report, the RVUs assigned to a healthcare service compare its value relative to other procedures or services and may differ depending on where the procedure or service is performed (i.e., non-facility or facility).[188] There are three types of RVUs—work, practice expense, and malpractice—each of which are adjusted by a geographic price cost index when calculating the total RVUs for a given procedure or service. The total fee for a service is then calculated as the product of the total RVUs and a conversion factor, which converts RVUs to dollars. The price of a given service will reflect the professional fee, and in some cases, a separate facility fee, each with their own RVUs.[189]

107. At the highest level, variation in Medicare prices across healthcare procedures and services, designated by procedure codes (more formally, Current Procedural Terminology or "CPT codes"), is derived from variation in RVUs assigned to those CPT codes. In addition, multiple CPT codes may exist for a given procedure or service (e.g., urinalysis), reflecting variation in how the procedure or service is performed across patients, providers, and clinical settings (e.g., location of an imaging test or duration of an examination). In some cases, CPT codes are specified further by modifiers (e.g., the procedure or service was more complicated than

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[187] *American Academy of Professional Coders*, "What are Relative Value Units (RVUs)?" December 30, 2020, available at https://www.aapc.com/practice-management/rvus.aspx.

[188] Non-facility typically refers to a free-standing physician's office. Facility can refer to an inpatient hospital, a hospital's outpatient department, an ambulatory surgery center, or a skilled nursing facility. *American Academy of Professional Coders*, "What are Relative Value Units (RVUs)?" December 30, 2020, available at https://www.aapc.com/practice-management/rvus.aspx. *See also*, Song Report, ¶¶29, 31.

[189] Song Report, ¶29.

normal or performed under unusual circumstances).[190] I discuss variation in CPT codes in more detail in **Section VI.B** below.

108. For commercially insured patients, the variation in prices can be substantial. Each commercial insurer typically negotiates a fee schedule with those providers within their insurance networks. For any given commercial insurer, prices can vary substantially across providers both in and out of network. Furthermore, different commercial insurers will negotiate different contracts for the same provider and may have different sets of in and out of network providers. Because commercial fee schedules are negotiated between two parties, they can vary by state, region, payer, and/or provider.[191] Recent research has demonstrated that variation in private insurance prices is the major source of variation in healthcare spending under private insurance, in contrast with variation in spending under Medicare which is driven by quantity variation.[192] Researchers, policy makers, and industry participants have not had access to the universe of private insurance prices for each service and provider, as such a data source does not exist.

1. Existing research on price variation

109. Conditional on a procedure or service being well defined (e.g., by a given CPT code with or without a modifier), studies have found high variability even in average procedure and service prices across payers and geographies. While this variation is evident in Figure 1 of Professor Song's report, it is not discussed in the text. Instead, Professor Song simply reports *average* ratios of commercial payments to Medicare payments, which are used in subsequent estimations.[193] A 2020 study analyzed variation separately for inpatient facility, outpatient facility, and professional fees and found that the ratio of total commercial payments to

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[190] RevenueXL, "What are CPT Modifiers?" April 9, 2021, available at https://www.revenuexl.com/blog/cpt-modifiers.

[191] *Axene Health Partners*, "Physician Fee Schedules: How Do They Compare and What's Next?" available at https://axenehp.com/physician-fee-schedules-compare-whats-next/.

[192] Cooper, Zack, *et al.,* "The Price Ain't Right? Hospital Prices and Health Spending on the Privately Insured," *The Quarterly Journal of Economics*, Vol. 134, No. 1, February 2019, pp. 51–107 at p. 102.

[193] Song Report, ¶¶22, 35.

counterfactual traditional Medicare payments was higher for the two types of facility fees (2.06 [inpatient]; 2.16 [outpatient]) than professional fees (1.63).[194] Ratios for all three fee types also varied considerably across states, as evidenced by state interquartile ranges of 0.35 (inpatient facility), 0.46 (outpatient facility), and 0.36 (professional). State ratios were estimated based on spending at the aggregate level (i.e., across patients and services) and therefore do not reflect variation that exists *within* states across these other dimensions. Results were robust over time, suggesting that average prices are not converging in a way that will reduce variation at the time the medical monitoring program would occur.[195] Studies have also found substantial price variation across metropolitan areas. A 2010 study of metropolitan healthcare markets in eight states found that average inpatient hospital payment rates of four large national commercial insurers ranged from 147 percent of Medicare to 210 percent of Medicare across markets.[196] Some outlier hospitals received even greater markups over Medicare: one hospital was paid almost five times Medicare rates for inpatient services, and another was paid over 7 times Medicare rates for outpatient services. The study found similarly extensive variation *within* markets for both types of services. A more recent analysis by the Health Care Cost Institute looked at 271 metropolitan areas in 48 states and found similarly high variation in commercial prices as a share of Medicare prices for professional services.[197]

110. Even within Medicare there is price variation between traditional Medicare (also referred to as fee-for-service Medicare) and Medicare Advantage (a privatized option where benefits are administered by private insurance companies rather than the federal government). A 2020 study of unique all-payer data spanning 38 US states found that after controlling for enrollee

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[194] Chernew, Michael E, *et al.*, "Wide State-Level Variation In Commercial Health Care Prices Suggests Uneven Impact Of Price Regulation," *Health Affairs*, Vol. 39, No. 5, May 2020, pp. 791–799.

[195] Chernew, Michael E, *et al.*, "Wide State-Level Variation In Commercial Health Care Prices Suggests Uneven Impact Of Price Regulation," *Health Affairs*, Vol. 39, No. 5, May 2020, pp. 791–799 at p. 795.

[196] The eight healthcare markets studied were: Cleveland, Indianapolis, Los Angeles, Miami, Milwaukee, Richmond, San Francisco, and rural Wisconsin. Ginsburg, Paul B., "Wide Variation in Hospital and Physician Payment Rates Evidence of Provider Market Power," *Center for Studying Health System Change*, November 2010, available at http://www.hschange.org/CONTENT/1162/.

[197] Johnson, Bill, *et al.,* "Comparing Commercial and Medicare Professional Service Prices," *Health Care Cost Institute*, August 13, 2020, available at https://healthcostinstitute.org/hcci-research/comparing-commercial-and-medicare-professional-service-prices.

and hospital mix, Medicare Advantage pays over 10 percent more than traditional Medicare for the five most common inpatient diagnoses.[198] In contrast, a 2017 study found that average prices paid for physician services were lower in Medicare Advantage relative to traditional Medicare.[199]

111. While commercial prices tend to exceed Medicare prices, prices paid by other payers can be below Medicare prices. For example, an analysis by the Congressional Budget Office found that healthcare services provided to veterans through the Veterans Health Administration ("VHA") could be more expensive if provided at Medicare prices (+16 percent for inpatient care; +11 percent for outpatient care).[200] This result stands in contrast to the following statement in Professor Song's report about the VHA and other federal health programs: "In general, these public programs pay health care providers Medicare prices."[201] The source Professor Song cites explains that the Department of Veterans Affairs ("VA") typically pays Medicare rates for services provided to veterans outside of VA medical facilities; however, payments for services rendered *within* the VHA system are only limited to be "no higher than Medicare".[202] Historically, Medicaid has also paid physicians lower fees than Medicare for the same services.[203] In 2019, Medicare physician fees averaged 72 percent of Medicare physician

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198 Fronsdal, Toren, *et al.*, "Variation in Health Care Prices Across Public and Private Payers," *Stanford Institute for Economic Policy Research*, September 2020, available at https://siepr.stanford.edu/publications/working-paper/variation-health-care-prices-across-public-and-private-payers.

199 Trish, Erin, *et al.,* "Physician Reimbursement in Medicare Advantage Compared with Traditional Medicare and Commercial Health Insurance," *JAMA Internal Medicine*, September 2017, Vol.177, No. 9, available at https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2643349.

200 Inpatient care excludes costs for nursing homes and rehabilitation facilities. *Congressional Budget Office*, "Comparing the Costs of the Veterans' Health Care System With Private-Sector Costs," December 2014, available at https://www.cbo.gov/sites/default/files/113th-congress-2013-2014/reports/49763-VA_Healthcare_Costs.pdf, p. 5.

201 Song Report, ¶25.

202 *Department of Veterans Affairs*, "Veterans Community Care Program, Final Rule," June 2019, Vol. 84, No. 108, pp. 26278–26310, available at https://www.federalregister.gov/documents/2019/06/05/2019-11575/veterans-community-care-program.

203 Zuckerman, Stephen, *et al.*, "Medical Physician Fees after the ACA Primary Care Fee Bump," *Urban Institute*, March 2017, available at https://www.urban.org/sites/default/files/publication/88836/2001180-medicaid-physician-fees-after-the-aca-primary-care-fee-bump_0.pdf.

fees for common procedures, 67 percent for primary care, and 80 percent for obstetric care.[204] Nevertheless, average price comparisons between insurers and payers may be highly problematic because of differences in coding incentives and differences in patient and provider populations under different payment arrangements.[205]

112. Prices charged to uninsured patients are often the highest prices.[206] As of January 2021, federal regulations require hospitals to publicly disclose "discounted cash prices" that are charged to patients who pay "cash (or cash equivalent) for a hospital item or service."[207] Researchers recently analyzed these prices for two common procedures—colonoscopies (one of Professor Song's identified services) and magnetic resonance imaging ("MRI") scans—and found that they varied substantially between three large hospitals.[208] Specifically, colonoscopy prices ranged from $1,273 to $1,929 and prices for a lower limb MRI ranged from $1,247 to $3,105. The authors considered the variation "striking" given the similarity of the hospitals, in terms of size, non-profit status, trauma certification, and academic affiliation, which suggests even greater variation may be observed in a more heterogeneous sample. In addition, discounted cash prices do not reflect "any charity care or bill forgiveness that a hospital may choose or be

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204 Young, Kerry D., "Medicaid Physician Fees Still Lag Medicare Payment Rates," *Medscape*, February 9, 2021, available at https://www.medscape.com/viewarticle/945509.

205 Kronick, Richard, "Projected Coding Intensity In Medicare Advantage Could Increase Medicare Spending By $200 Billion Over Ten Years," *Medicare Advantage*, February 2017, available at https://www.healthaffairs.org/doi/full/10.1377/hlthaff.2016.0768, pp. 320–327 at p. 321. *See also*, Graves, John A., *et al.,* "Breadth and Exclusivity of Hospital and Physician Networks in US Insurance Markets," *JAMA Network Open*, Vol. 3, No. 12, December 17, 2020, pp. 1–13, at p. 10; Keisler-Starkey, Katherine, and Lisa N. Bunch, "Health Insurance Coverage in the United States: 2020," *census.gov,* September 2021, available at https://www.census.gov/content/dam/Census/library/publications/2021/demo/p60-274.pdf.

206 Evans, Melanie, Anna Wilde Mathews, and Tom McGinty, "Hospitals Often Charge Uninsured People the Highest Prices, New Data Show," *The Wall Street Journal*, July 6, 2021, available at https://www.wsj.com/articles/hospitals-often-charge-uninsured-people-the-highest-prices-new-data-show-11625584448.

207 *Centers for Medicare and Medicaid Services*, "Medicare and Medicaid Programs: CY 2020 Hospital Outpatient PPS Policy Changes and Payment Rates and Ambulatory Surgical Center Payment System Policy Changes and Payment Rates. Price Transparency Requirements for Hospitals to Make Standard Charges Public," November 27, 2019, available at https://www.federalregister.gov/documents/2019/11/27/2019-24931/medicare-and-medicaid-programs-cy-2020-hospital-outpatient-pps-policy-changes-and-payment-rates-and#p-1030.

208 Morgane, Mouslim, and Morgan Henderson, "How New Data On Hospital 'Discounted Cash Prices' Might Lead To Patient Savings," *Health Affairs*, November 8, 2021, available at https://www.healthaffairs.org/do/10.1377/forefront.20211103.716124/full/.

required to apply to a particular individual's bill."[209] Discounts given to uninsured patients as part of charity care policies have been shown to vary both across hospitals and within hospitals by patient income.[210] Furthermore, those who qualify for financial aid do not always receive it, and in some cases, may not even know it is available.[211] Given the above evidence, prices of monitoring services for proposed class members who are or may become uninsured are likely to be similarly variable to those with insurance.

2. Pricing variation observed in selected data sources

113. My empirical analyses further demonstrate the substantial variation in prices paid by commercial insurers as well as prices faced by uninsured patients. For example, **Figure 8** below characterizes the variation in the outpatient prices that Massachusetts General Hospital ("MGH"), Professor Song's employer, has negotiated with commercial insurers for the six monitoring services that Professor Song identified in Table 6 of his report. For my analyses, I rely on the same procedure codes (CPT/HCPCS codes) specified by Professor Song in his report. This price variation is extensive. In fact, the 95th percentile price (i.e., the price that is higher than 95 percent of all prices negotiated) is 218 percent to 429 percent higher, or about 2 to 4 times higher, than the 5th percentile price (i.e., the price that is higher than only 5 percent of all negotiated prices) charged by MGH for outpatient services for all of the monitoring services considered by Professor Song.

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209 *Centers for Medicare and Medicaid Services*, "Medicare and Medicaid Programs: CY 2020 Hospital Outpatient PPS Policy Changes and Payment Rates and Ambulatory Surgical Center Payment System Policy Changes and Payment Rates. Price Transparency Requirements for Hospitals to Make Standard Charges Public," November 27, 2019, available at https://www.federalregister.gov/documents/2019/11/27/2019-24931/medicare-and-medicaid-programs-cy-2020-hospital-outpatient-pps-policy-changes-and-payment-rates-and#p-1030.

210 McGinty, Tom, Melanie Evans, and Anna Wilde Mathews, "Methodology: How the WSJ Analyzed Hospital Pricing Data," *The Wall Street Journal*, July 6, 2021, available at https://www.wsj.com/articles/methodology-how-the-wsj-analyzed-hospital-pricing-data-11625583571.

211 Thomas, Wendi C, "The Nonprofit Hospital That Makes Millions, Owns a Collection Agency and Relentlessly Sues the Poor," *ProPublica*, June 27, 2019, available at https://www.propublica.org/article/methodist-le-bonheur-healthcare-sues-poor-medical-debt. *See also*, Evans, Melanie and Anna Wilde Mathews, "Medical-Debt Charity to Buy, Wipe Out $278 Million of Patients' Hospital Bills," *The Wall Street Journal*, June 15, 2021, available at https://www.wsj.com/articles/medical-debt-charity-to-buy-wipe-out-278-million-of-patients-hospital-bills-11623762001; Kiel, Paul, "From the E.R. to the Courtroom: How Nonprofit Hospitals are Seizing Patients' Wages," *ProPublica*, December 19, 2014, available at https://www.propublica.org/article/how-nonprofit-hospitals-are-seizing-patients-wages.

Figure 8. MGH outpatient pricing for Professor Song's proposed procedures 2021

CPT/HCPCS Code	5th Percentile MGH Price Negotiated with an Insurer	95th Percentile MGH Price Negotiated with an Insurer	95th as % of 5th Percentile
81001 (Urinalysis)	$10	$44	429%
85025 (Complete blood count)	$27	$118	429%
99214 (30-39 minute office visit)	$106	$422	399%
71271 (Low-dose chest CT scan)	$478	$1,041	218%
43235 (Esophagogastroduodenoscopy)	$482	$2,069	429%
G0121 (Colonoscopy)	$783	$3,359	429%

Notes:

[1] Analysis is limited to outpatient prices.

[2] The MGH data record services according to MGH's procedure codes. For five of the above CPT/HCPCS codes, there is exactly one MGH procedure code associated with the code. However, in the case of CPT code 99214, MGH has three separate procedures associated with that CPT code. One of these MGH procedure codes is associated with psychiatric visits, so it is excluded from the analysis.

Source: MGH CMS-Required Hospital Charge Data (only includes commercial insurers), available at https://www.massgeneral.org/notices/billing/CMS-required-hospital-charge-data.

114. This substantial heterogeneity in commercial insurer prices is also evident in the OptumHealth data summarized in **Figure 9**. The OptumHealth data include over 19,700 patients who received affected valsartan and underwent at least one of the at-issue monitoring services in 2016 (the last full year of the data used for the analysis). The data include claims for the specified screening services and the total amount paid by the patient and health insurer. As demonstrated in **Figure 9**, the prices charged by providers for commercially insured patients vary extensively for each of the proposed monitoring services when evaluated for each CPT code. For instance, the 5th percentile of the prices for colonoscopies was $212, whereas the 95th percentile was $1,911, approximately nine times larger.

Figure 9. OptumHealth commercial pricing for Professor Song's proposed procedures 2016

CPT/HCPCS Code	No. of Patients	5th Percentile	25th Percentile	75th Percentile	95th Percentile	Median	Range 25th to 75th
81001 (Urinalysis)	3,851	$1.30	$2.41	$6.00	$28.80	$3.00	$3.59
85025 (Complete blood count)	8,453	$3.06	$5.51	$17.00	$57.00	$7.82	$11.49
99214 (30-39 minute office visit)	17,866	$67.00	$96.00	$135.23	$197.00	$112.66	$39.23
43235 (Esophagogastroduodenoscopy)	114	$61.13	$133.80	$445.00	$1,512.00	$197.99	$311.20
G0121 (Colonoscopy)	172	$212.00	$243.00	$814.00	$1,911.00	$430.00	$571.00

Notes:

[1] Total price includes the deductible, copay, coinsurance, paid and coordination of benefits amounts for the respective procedures.

[2] Patients were required to be under 65 years of age at the date of service, as patients who are 65 years old or older may have their medical benefits partially reimbursed by Medicare. Age was computed from July 1st of the birth year to the date of service.

[3] Analysis includes inpatient (facility) and outpatient (non-facility) claims for services performed in 2016 for patients who took affected valsartan (see footnote 23) in 2012-2017. Professor Song only reports non-facility (outpatient) prices for the monitoring services that he identifies (Song Report, ¶38, Table 6).

Source: OptumHealth data.

115. Uninsured patients also face substantial variation in the prices they are charged for a given medical service. To characterize this variation, I rely on Medicare Public Use data in which healthcare providers report, among other information, the number of claims and average charged amount for those claims by provider, place of service, and year.[212] While Medicare does not reimburse providers according to charges, it requires that providers report average charges, which reflect the default price that the provider would likely charge an uninsured patient for the service.[213] I use the 2019 Medicare Public Use data to analyze the charged amounts for those procedures proposed by Professor Song. **Figure 10** shows the substantial

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[212] *Centers for Medicare and Medicaid Services*, "Medicare Physician & Other Practitioners - by Provider and Service," available at https://data.cms.gov/provider-summary-by-type-of-service/medicare-physician-other-practitioners/medicare-physician-other-practitioners-by-provider-and-service.

[213] *Centers for Medicare and Medicaid Services*, "Medicare Provider Utilization and Payment Data, Physician and Other Supplier PUF: Frequently Asked Questions," May 23, 2019, available at https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Medicare-Provider-Charge-Data/Downloads/Physician_FAQ.pdf ("Does anyone actually pay the submitted charges in the Physician and Other Supplier PUF? In the private market, patients with comprehensive coverage often do not pay full charges because insurance companies negotiate better payment rates for their policy holders. Conversely, individuals with inadequate or no insurance coverage could be billed the full charge for the service or procedure. These individuals might not be able to take advantage of a lower payment rate negotiated by a private insurance company. The Medicare fee-for-service program sets payment rates for covered services.").

variation in average charged amounts by different providers for six CPT/HCPCS codes identified by Professor Song for those procedures.[214] For instance, the 5th percentile of average charges for a urinalysis test was $6, whereas the 95th percentile was $48. Wide ranges are also observed for the other proposed procedures, particularly for colonoscopies where the 5th percentile is $421 and the 95th percentile is almost nine times that amount ($3,745).

Figure 10. Medicare charged amounts for Professor Song's proposed procedures 2019

CPT/HCPCS Code	5th Percentile Charged Amount	95th Percentile Charged Amount	95th as % of 5th Percentile
81001 (Urinalysis)	$6	$48	855%
85025 (Complete blood count)	$14	$55	404%
99214 (30-39 minute office visit)	$117	$361	309%
G0297 (Low-dose chest CT scan)	$88	$806	916%
43235 (Esophagogastroduodenoscopy)	$286	$1,900	664%
G0121 (Colonoscopy)	$421	$3,745	890%

Note: The data report the average charged amounts across all procedures performed under a given CPT/HCPCS code at each provider service location. The percentiles reported in this figure are the percentiles of average charged amount weighted by the number of procedures performed at the provider location.

Source: Medicare Public Use Files

116. Moreover, the Medicare charges described above do not reflect the full extent of variation in prices charged to uninsured patients. Uninsured patients treated by the same provider at the same service location may face different prices, as some patients may negotiate individual discounts or payment plans. For instance, large laboratory providers offer payment plans and financial assistance programs for patients facing financial hardship.[215] Likewise, MGH offers

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[214] This analysis uses HCPCS code G0297 instead of 71271 for the low-dose chest CT scan, because G0297 was the code for that procedure until 2021. *See, e.g., Centers for Medicare and Medicaid Services*, "Medicare HETS 270/271 - Information Bulletin - HETS HCPCS Code Change Effective January 1, 2021," December 18, 2020, available at https://www.cms.gov/research-statistics-data-and-systemscms-information-technologyhetshelpmcare-notification-archive/medicare-hets-270271-information-bulletin-hets-hcpcs-code-change-effective-january-1-2021.

[215] *Quest Diagnostics*, "Quest Diagnostics Patient Assistance Program," available at http://www.carilionlabs.com/home/about/corporate-citizenship/community-giving/assistance/. *Labcorp*, "Payment Programs," available at https://www.labcorp.com/frequently-asked-questions/patient/billing-insurance/payment-programs.

payment plans and discounts for certain patients.[216] Thus, total spending on medical procedures performed on uninsured patients may not be equal to what would be implied by average Medicare charges.

117. Finally, Professor Song proposes estimates for the price of screening services based on national averages, and not average prices specific to members of the proposed class. Even if Professor Song's analysis were able to identify accurate national average prices for screening services today and in the future, those prices would not necessarily reflect the average price paid by members of the proposed class. Members of the class are not randomly drawn from the nation as a whole, but rather differ from an average, non-valsartan patient, in important ways. As mentioned earlier, valsartan patients (whether they took affected or non-affected valsartan) tend to be older, more likely to have diabetes, and more likely to have cancer. Given the substantial price variation that I summarize above, there is no reason to believe that the average prices experienced by proposed class members is the same as the average prices experience by the nation as a whole. Furthermore, these prices may vary based on numerous other factors, such as the negotiating power between specific insurers and providers, patient's location, the quality and location of the place of service, and the type of service provider (facility v. non-facility). Even if Professor Song's analysis were using accurate average prices for services nationally, they may not be the appropriate average prices that would be incurred by the proposed class members.

B. Variation in medical services

118. The spending associated with CPT codes is not a good proxy for the spending actually incurred for some procedures—e.g., independent laboratories such as Labcorp and Quest often offer

[216] *Mass General Brigham*, "Financial Assistance," available at https://www.massgeneralbrigham.org/patient-information/financial-assistance.

multiple related-but-different tests under the same CPT code.[217] For uninsured or out-of-pocket patients, these different tests can have different list prices even though they all have the same CPT code. Therefore, the average spending by CPT code could be substantially different from the true spending for some of those tests.

119. Even for patients whose payer reimburses by CPT or HCPCS code, and accepting, for the sake of argument, the factually implausible scenario under which Professor Song's six procedures would be appropriate for some proposed class of patients without appropriate clinical consideration of their individualized circumstances, it is still the case that different patients would receive different procedures with different CPT codes and corresponding spending. This is because for each of the six procedures Professor Song considers, there are several different CPT or HCPCS codes associated with similar procedures. Professor Song knows that this is a crucial determination and he just "select[s] a fairly common CPT code" for a service that has multiple CPT codes.[218] Professor Song has not explained how a class-wide methodology would handle this variation. For example:

- Urinalysis: There are 11 different CPT codes associated with a urinalysis. While some of these codes are unlikely to be used as part of a cancer screening (for example, one of these codes is for a pregnancy test), many of the tests screen for similar analytes using different methodologies.[219]
- Complete Blood Count: There are two CPT codes associated with a complete blood count. The difference is that the 85025 CPT code Professor Song considers includes a

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[217] For instance, Labcorp's website lists at least three different complete blood count tests corresponding to CPT code 85025. *See, e.g., Labcorp*, "Complete Blood Count (CBC) With Differential," available at https://www.labcorp.com/tests/005009/complete-blood-count-cbc-with-differential. *See also, Labcorp*, "Neutrophil to Lymphocyte Ratio (NLR), Complete Blood Count (CBC) With Differential and Platelet," available at https://www.labcorp.com/tests/005013/neutrophil-to-lymphocyte-ratio-nlr-complete-blood-count-cbc-with-differential-and-platelet; *Labcorp*, "Liver Fibrosis Risk Profile With Hepatic Function Panel, Complete Blood Count (CBC) With Differential, FIB-4, and APRI," available at https://www.labcorp.com/tests/402145/liver-fibrosis-risk-profile-with-hepatic-function-panel-complete-blood-count-cbc-with-differential-fib-4-and-apri.

[218] Song Report, ¶33.

[219] *American Medical Coding*, "CPT code for Urinalysis: Basic Coding Guidelines for Coders," November 3, 2019, available at https://www.americanmedicalcoding.com/cpt-code-for-urinalysis/.

differential white blood cell count in addition to the panel of other blood counts, whereas the CPT code 85027 does not.[220] In addition, each of the components of either of the individual tests included in those panel tests can also be ordered individually, and each individual test has its own CPT code.[221]

- Office Visit: There are 11 different CPT codes and one HCPCS code for evaluation and management office visits depending on the duration of the visit and whether the patient is a new or established patient. Professor Song assumes that patients will require such an office visit each year and considers the office visit corresponding to CPT code 99214 for an established patient visit of 30-39 minutes.[222] However, that CPT code is only one of many that can be used for an evaluation and management office visit. First, there are four other codes that cover evaluation and care office visits of different durations less than 55 minutes. Second, there are five CPT codes for evaluation and management office visits of less than 75 minutes for new patients. In addition, there is a separate CPT code and a separate HCPCS code for prolonged evaluation and care visits.[223] Thus, unless a patient is seeing a doctor they have seen previously and the visit lasts more than 29 but less than 40 minutes, then the CPT code Professor Song considers would not appropriately capture the spending for that visit.

- Low-Dose Chest CT scan: While there is only one CPT code associated with low-dose chest CT scans,[224] there are three other CPT codes associated with standard-dose

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220 *American Medical Coding*, "CPT code 85025 & 85027 Coding Guide," February 20, 2020, available at https://www.americanmedicalcoding.com/cpt-code-85025-85027/.

221 *Medicare Payment and Reimbursement*, "Complete Blood Count (CBC)," available at https://medicarepaymentandreimbursement.com/2010/07/complete-blood-count-cbc-testing-cpt.html. *See also*, *See also,* Painter, Scott, "CPT Code 85025," *PRSnetwork*, October 1, 2018, available at https://info.prsnetwork.com/cpt-code-85025/.

222 Song Report, ¶32, Table 6. *See also, American College of Surgeons*, "Office/Outpatient E/M Codes," available at https://www.facs.org/advocacy/practmanagement/em-education/codes.

223 *American College of Surgeons*, "Office/Outpatient E/M Codes," available at https://www.facs.org/advocacy/practmanagement/em-education/codes.

224 Rajagopal, Rajeev, "CPT Code Changes for Radiology in 2021," *Outsource Strategies International*, December 28, 2020, available at https://www.outsourcestrategies.com/blog/cpt-code-changes-for-radiology-in-2021.html.

chest CT scans.[225] Should a patient require one of the standard-dose procedures for whatever reason, that may mean that the patient would receive a chest CT scan under a different CPT code than the one Professor Song considers.

- Upper Endoscopy: There are many CPT codes associated with upper endoscopies, and many of them focus on different organs. For instance, the CPT code considered by Professor Song covers an esophagogastroduodenoscopy examining the esophagus, stomach, and duodenum.[226] However, there are other endoscopy procedures which focus primarily on the esophagus or on the liver and bile duct. Among the many CPT codes associated with esophagogastroduodenoscopies, many of them are not intended for screening, but it is possible that the screening component could be performed alongside another procedure such as dilation of the esophagus or removal of a foreign object.[227]

- Screening Colonoscopy: There are 15 CPT codes and HCPCS codes associated with colonoscopies. There are two different HCPCS codes that can be used for a screening colonoscopy performed on a Medicare patient. The G0121 code is used for patients that Medicare does not deem high risk, while the G0105 code is used for patients deemed high risk due to factors including inflammatory bowel disease and family or personal history of colorectal cancer.[228] There are also a number of CPT codes for colonoscopies in general.[229] Although there is only one CPT code for a screening colonoscopy, it is possible that one of the other types of colonoscopies could be performed and also cover the screening element as a secondary objective.

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225 *MedLearn Media*, "Chest CT - Correct Coding and Billing," April 22, 2020, available at https://www.medlearnmedia.com/insights/chest-ct-correct-coding-and-billing/.

226 Song Report, ¶32, Table 6.

227 Brill, Joel, Daniel DeMarco, and Glenn Littenberg, "CPT Coding Updates," *American Society for Gastrointestinal Endoscopy*, 2014, available at https://www.asge.org/docs/default-source/practice-support/coding/074a7ebc-2222-4d00-94eb-701d6a8e0ec6.pdf.

228 *American Gastroenterological Association*, "Coding FAQ - Screening Colonoscopy," available at https://gastro.org/practice-guidance/reimbursement/coding-faq-screening-colonoscopy/.

229 *American Society for Gastrointestinal Endoscopy*, "Colonoscopy - CPT Codes," 2017, available at https://www.asge.org/docs/default-source/coding/colonoscopy_2018-coding-sheet.pdf?sfvrsn=3a2ca050_4.

120. For some of the screenings Professor Song considers, even if there were no dispute about which procedures a patient required, it would still be unclear which CPT code would be applied for individual patients. For instance, the same patient might be coded under different CPT codes for an evaluation and management visit depending on the precise length of the visit or whether they were a current or new patient at their service provider. As another example, two Medicare patients receiving screening colonoscopies might be coded under different CPT codes depending on whether they have other risk factors for colon cancer. Moreover, it is possible that patients who also require additional procedures such as tissue extraction or removal of foreign objects could receive an upper endoscopy or screening colonoscopy that would be coded under a different CPT code from the one Professor Song considers. In all these cases, two patients undergoing the same general screening considered by Professor Song would incur different spending associated with different procedure codes. Professor Song does not account for this variation in his class-wide methodology.

C. Variation in cost-sharing

121. **Section VI.A** and **VI.B** describe sources of variation in total prices paid. When a patient is insured, the total price is often shared between the patient and the insurer. The share of the total price paid by a patient versus insurer will vary across insurers, across patients, and will vary for any given patient across covered benefits, the provider the patient selects (i.e., in network or out of network), and other plan provisions.[230] Professor Song acknowledges there is typically cost-sharing when patients are insured.[231]

122. Patients contribute to the cost of the healthcare they use through cost-sharing such as co-payments (i.e., fixed dollar amounts), co-insurances (i.e., a percentage of the price for service), and deductibles (i.e., an amount that must be paid before most services are covered by the

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[230] Cox, Cynthia, et. al., "Price transparency and variation in U.S. health services," *Health System Tracker*, January 13, 2021, available at https://www.healthsystemtracker.org/brief/price-transparency-and-variation-in-u-s-health-services/.

[231] Song Report, Table 6 ("Prices reflect the sum of both the insurer share and patient cost-sharing per unit of a service.").

plan).[232] Each of these three types of arrangements can vary with respect to the degree of patient cost sharing. Co-payments shield patients from some variation in prices, but the amount of co-payment (e.g., $50 or $100) can vary across patients, and for a patient depending on the type of service and whether the provider is in-network or out of network. For co-insurance on the other hand, the patient's payment can vary depending on the price charged by the provider and the percent of the price the patient is obligated to pay, which can vary across insurers, services, and whether the provider is in-network or out-of-network. Finally, for a patient subject to a deductible, they pay the full price of the provider's charge up to the amount of their deductible, after which a co-payment co-insurance payment may be required, or the insurer may pay the full amount after the deductible. Again, the patient share will vary depending on the deductible amount and the payment sharing for amounts above the deductible, and those factors can vary across patients, insurers, and services. Deductibles may apply to a specific service or can apply to the patient's cumulative medical costs and are reset at the start of each plan year.

123. Within Medicare, cost-sharing varies according to the type of Medicare the patient has. In traditional Medicare, patients face standardized cost-sharing for both Part A (inpatient care) and Part B (outpatient) benefits.[233] However, patients may opt to reduce their cost-sharing through a supplemental or "Medigap" plan. Medigap plans are sold and administered by private health insurance companies and help patients enrolled in traditional Medicare with out-of-pocket costs resulting from co-payments, co-insurance, and deductibles.[234] Thus, cost-sharing will vary across patients in traditional Medicare depending on whether they have a

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232 *Kaiser Family Foundation*, "2020 Employer Health Benefits Survey," October 8, 2020, available at https://www.kff.org/report-section/ehbs-2020-section-7-employee-cost-sharing/.

233 *Medicare.gov*, "Medicare costs at a glance," available at https://www.medicare.gov/your-medicare-costs/medicare-costs-at-a-glance.

234 *Medicare.gov*, "What's Medicare Supplement Insurance (Medigap)?", available at https://www.medicare.gov/supplements-other-insurance/whats-medicare-supplement-insurance-medigap.

Medigap plan, and if so, the generosity of the plan.[235] In Medicare Advantage, cost-sharing is not standardized and will therefore vary across patients by plan.[236]

124. As I mention above, patient preferences play a major role in determining whether screening for cancer is appropriate and indicated for each individual patient. Patient preferences will also be strongly related to the insurance and cost-sharing arrangement that each individual patient participates in.[237] Therefore, the cost of a monitoring program that considers both whether screening is indicated and the cost that each patient will face for screening will depend on the interaction between the two. Failure to consider this interaction will necessarily mistake the aggregate cost to patients of medical monitoring.

125. It is my understanding that the relevant cost in this matter is to the members of the proposed class, who are patients. Professor Song's "common methodology" looks at total price for services, which includes not just the amount paid by patients, but also the amounts paid by commercial insurers, state governments, and the Federal government. As a results, the prices considered by Professor Song would grossly overstate the spending relevant for patients.

126. Not only does Professor Song fail to account for the portion of the total price paid by patients—i.e., the types of payers who are members of the proposed class—but variation in patient cost sharing arrangements further exacerbates the substantial variation in prices paid for screening services. The variability in total prices, variability in patient cost-sharing arrangement, and individualized nature of which screening services may apply to any individual member of the proposed class all speak to the need for individualized inquiry to determine which members of the proposed class may incur future costs for screening as a result of affected valsartan use and the costs of such screening services (if any) to those patients. The

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235 Patients in traditional Medicare may also elect to enroll in Part D benefits with a prescription drug plan (PDP). PDPs are also administered by private insurers and vary in the degree of cost-sharing required. *See, e.g., Medicare.gov*, "How to Compare Medigap Policies," available at https://www.medicare.gov/supplements-other-insurance/how-to-compare-medigap-policies.

236 *Centers for Medicare and Medicaid Services*, "Understanding Medicare Advantage Plans," available at https://www.medicare.gov/Pubs/pdf/12026-Understanding-Medicare-Advantage-Plans.pdf, pp. 4–7.

237 Salampessy, Benjamin H., *et al.*, "The effect of cost-sharing design characteristics on use of health care recommended by the treating physician; a discrete choice experiment," *BMC Health Services Research*, 2018.

individualized nature of this inquiry is all the more important because there is no data source that would contain all of the necessary information to determine these patient costs.

D. Uncertainty in future prices, services, insurance coverage, and technology

127. The variation in prices, medical screening services, and cost-sharing mentioned above will also change over time and will be different in the future in ways that are not possible to anticipate today. Each of these factors, the screening services (if any) applicable to any given proposed class member, the provider cost for those services, and the patient cost sharing component, will vary substantially across proposed class members. Furthermore, the variability of these factors is further complicated when projecting into the future. Professor Song acknowledges that there are some "additional factors that affect prices or quantities of care [that] may also be incorporated" into a common methodology.[238] Yet, he does not enumerate the many factors that need to be considered, provides no evidence of how such factors would be calculated, and does not identify any data source that would facilitate a class-wide methodology of future considerations. Moreover, Professor Song does not consider the time frame over which the medical monitoring services will be provided and how far into the future it would be necessary to anticipate the myriad changes in all these factors. Uncertainty will be greater the further into the future projections are made. Below are a few important considerations that highlight the uncertainty of these factors in the future.

128. In terms of prices, there is consistent effort in the medical community to improve efficiency and align incentives to ensure quality care for patients. Among other things, this effort necessitates changes to provider reimbursement and the prices of services. For example, the Relative Value Scale Update Committee ("RUC") is a professional, multi-specialty committee charged with making annual recommendations to the Centers for Medicare & Medicaid Services ("CMS") regarding RVUs (as noted earlier, RVUs are a foundation for determining physician fees within Medicare). Since its inception in 1992, the RUC has submitted over 7,400 relative value recommendations related to new codes, revised codes, and potentially misvalued

[238] Song Report, ¶42.

codes.[239] The RUC includes a specific workgroup dedicated to identifying misvalued procedure codes using objective screening criteria (e.g., high utilization growth, high expenditure, site-of-service shifts).[240] The "evaluation and management" category of CPT codes are also likely to evolve over time, as more patient visits are conducted virtually (known as telemedicine) and/or with non-MD providers.[241] Price changes for such codes will be relevant to the pricing of a medical monitoring program to the extent that screening procedures are performed by non-MD providers and/or test results are communicated to patients through different mediums (e.g., in person, over phone, or by video conference).

129. Additionally, Professor Song notes the ratio of private insurance prices to Medicare prices has changed dramatically over time.[242] Professor Song points to a study that analyzed the growth in private insurance prices over five years.[243] While this trend could continue, it could also slow or change in ways that are difficult to anticipate, depending on market dynamics, future regulations, or other factors. The longer the timeline, the more uncertain such changes are.[244] Professor Song even admits that "[a]s the time horizon of estimation lengthens, prices may also evolve due to regulation or market forces."[245]

130. Separately, the structure and composition of health insurance may change over time as economic and demographic factors shift the share of people covered by Medicare, Medicaid,

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239 *American Medical Association*, "2022 RVS Update Process: AMA/Specialty Society," 2021, available at https://www.ama-assn.org/system/files/ruc-update-booklet.pdf.

240 *American Medical Association*, "2022 RVS Update Process: AMA/Specialty Society," 2021, available at https://www.ama-assn.org/system/files/ruc-update-booklet.pdf.

241 Lloyd, Stacy L, "A Review of Telehealth Trends: Informing the Future of Virtual Care," *American Medical Association*, 2020, available at https://www.ama-assn.org/system/files/2021-02/emerging-topics-webinar-telehealth-slides.pdf, p. 6 ("The tools and guidelines being created not are already helping many to use telemedicine and will continue to help define its role at this moment, and shape the future of physician practice."). *See also*, Hargraves, John, and Amanda Frost, "Trends in Primary Care Visits," *Health Care Cost Institute*, October 2018, available at https://healthcostinstitute.org/hcci-research/trends-in-primary-care-visits, ("a decline in visits to primary care physicians was partially offset by increases in visits to nurse practitioners and physicians assistants," and Figure 1).

242 Song Report, ¶40.

243 Song Report, ¶40. *See also*, *Health Care Cost Institute*, "HCCI's Health Care Cost and Utilization Reports," February 2020, available at https://healthcostinstitute.org/annual-reports/2020-02-13-18-20-19.

244 Professor Song does not indicate how many years the medical screenings should occur.

245 Song Report, ¶40.

or commercial insurers. Furthermore, government initiative and programs may change in ways that make certain types of insurance more or less accessible to different portions of the population. It is unclear what the composition of health insurance will be in the future.[246] This composition will impact what the prices members of the proposed class will face for any given screening procedure. Professor Song even states that his calculation will have to account for a "given health insurance mix" but provides no insight on how to make such quantification.[247] While he does acknowledge that there will be a shift from commercial insurance to Medicare coverage as patients age, there are still many other insurance options and composition effects that need to be considered that Professor Song does not explain.[248] What and which medical screening services, are covered by different insurers could change over time, especially with continued advancement in medical technology.

131. In addition to uncertainty in future prices and insurance composition, there is uncertainty in the innovation of medical technology and what types of screening services will be available in the future. As new advances in screening technologies emerge, the individualized cancer screening considerations for each patient will evolve, which will have implications for the extent to which use of affected valsartan will impact cancer screening decisions for any individual member of the proposed class and the cost of screening services for that member.

VII. DR. CONTI'S CLAIM THAT AFFECTED VALSARTAN IS WORTHLESS IGNORES THE THERAPEUTIC BENEFITS RECEIVED BY PATIENTS

132. Determining the value received from taking a drug is inherently a patient-by-patient assessment, not unlike determining the need for screening. The degree to which a drug provides value to a patient will vary across patients given their individualized situation, including their individual medical history, lifestyle, and underlying conditions. Different patients will

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246 U.S. Census Bureau, "Health Insurance Coverage in the United States: 2020," issued September 2021, available at https://www.census.gov/content/dam/Census/library/publications/2021/demo/p60-274.pdf, at p. 1 ("Year to year, the rate of health insurance coverage and the distribution of coverage types may change due to economic trends, shifts in the demographic composition of the population, and policy changes that affect access to care.").

247 Song Report, ¶42.

248 Song Report, ¶41.

experience different levels of efficacy, risks, and side effects that must also be considered to determine value. In the proposed economic loss class, many patients were treated with affected valsartan and received its therapeutic benefit treating their hypertension and/or heart failure. As I demonstrate below, from both a medical and economic perspective, it is clear that affected valsartan administered to patients was not "worthless" to all members of the proposed economic loss class as Dr. Conti claims.[249]

133. Dr. Conti's assertion that the affected valsartan products were "worthless" fails to consider the value patients and TPPs in the proposed economic loss class received from the administration of affected valsartan. Rather, her assessment that the product was "worthless" rests largely on her claim that there would be no supply of the drug in the but-for world rather than on the value actually received by patients and TPPs.[250] The implementation of her approach relies on faulty reasoning. Dr. Conti asserts that "[a]ccording to economic theory, for a consumer product to have economic value, demand for the product must exist and supply must be allowed to meet demand."[251] However, the demand curve alone speaks to a product's economic value and is based on each patient's and TPP's willingness to pay for a drug.[252] Consider a pill that cures cancer. There is no supply for such a pill as one has not been invented yet, but it is certainly possible to consider the patient and TPP's willingness to pay for such a pill and the inherent economic value such an innovation would provide. An approach predicated on the assumption that value requires a "legitimate supply" is the wrong framework for evaluating economic value in this case.[253] The reality is that patients of the proposed economic loss class *did* receive affected valsartan. Consequently, it is necessary to evaluate the value to them and their TPPs of the affected valsartan product that they received.

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[249] Conti Report, ¶39.

[250] Conti Report, ¶¶39–46.

[251] Conti Report, ¶43.

[252] Pindyck, Robert S. and Daniel L. Rubinfeld, *Microeconomics*, 2009, Seventh ed., Upper Saddle River, New Jersey: Prentice Hall, at pp. 132-135.

[253] Conti Report, ¶44.

134. To correctly consider this value, one must first consider that a positive anticipated economic value of the affected valsartan existed at the time the product was purchased (otherwise the physician would not have prescribed valsartan, and the patient and TPP would not have paid for valsartan). I will call the value of the affected valsartan at the time of purchase, prior to information about NDMA and NDEA risks, the *ex-ante value*. This ex-ante value depends on a host of individualized factors, which together inform the expected efficacy of the affected valsartan for treating the patient's condition. Such factors may include the severity of the treated condition (i.e., heart failure or hypertension), comorbidities (e.g., diabetes, renal impairment), side effects expected from alternative treatments, and idiosyncratic responses of blood pressure, heart function, or left ventricular remodeling that some patients may exhibit for valsartan relative to other treatments. Many patients and providers also recognize that there are often unknown risks when taking a medication. Consequently, the ex-ante value also incorporates the possibility of later revelations of risks.

135. One must then consider the change from the *ex-ante value* to the *ex-post value* of the affected valsartan after information becomes available on NDMA and NDEA risks. Our current state of knowledge is that the concentration of nitrosamine impurities varied widely across affected valsartan products. The extent to which this information will imply a lower ex-post value will depend on an individualized assessment of the patient's circumstances, which I elaborate upon below. After all of these considerations, the resulting ex-post value may be lower than the ex-ante value for some patients and TPPs, but certainly is not zero for all patient and TPP members of the proposed economic loss class. For example, some proposed class members who took valsartan made by a manufacturer known to have impurities in only some lots may have been exposed to no impurities whatsoever. These patients will suffer no decrease in their value of valsartan if they know (or learn) their prescriptions were from unaffected lots. As another example, patients with severe heart failure and a resulting low life expectancy would have arguably no decrease in their value of valsartan from the revelation of a cancer risk in the distant future.

136. Many patients who take valsartan have serious medical conditions that cannot go untreated. As such, the therapeutic benefits of valsartan for treating these medical conditions can be substantial. To my knowledge, there is no evidence that the efficacy of valsartan was

compromised for the affected valsartan products. As such, many of the patients who took affected valsartan received the therapeutic benefits associated with valsartan generally. In my analysis of the OptumHealth data from 2012-2017, I find that approximately a third of patients took affected valsartan for over a year and 16 percent of patients took affected valsartan for over two years, suggesting evidence of positive value from taking affected valsartan.[254] Such observed long-term use of valsartan is consistent with patients having received therapeutic benefits from the drug. Moreover, in some cases, a physician may have been able to confirm the therapeutic benefits of valsartan (including the affected valsartan products) through tracking patients' blood pressure, and objectively measuring whether valsartan provided value to patients being treated for hypertension.

137. Given the therapeutic benefits patients and TPPs received from the affected valsartan, assessing whether, and to what extent, the ex-post value is lower than the ex-ante value is a matter of individualized inquiry and cannot be done on a class-wide basis. The relevant consideration is that some patients may have been exposed to a marginally higher level of risk of cancer, than originally anticipated by taking the affected valsartan. This additional risk may reduce the economic value that patients received from the affected valsartan. The degree of reduction depends on at least two factors. First, it depends on just how much their cancer risk increased (i.e., the level of impurities within the affected valsartan they took). Second, any reduction in economic value depends on a patient's level of risk *aversion,* which has been shown to vary across individuals.[255] For a given objectively estimated increase in risk, the economic value will be reduced by a greater amount for someone who is more risk averse.

138. As I described in **Section III.B** even the FDA's own risk assessment indicates an extremely low potential risk of cancer associated with affected valsartan, and many members of the proposed economic loss class would have been exposed to far lower levels of NDMA and NDEA than considered by the FDA. As a result, most proposed class members face little or no

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[254] See footnote 152 for methodology.

[255] *See, e.g.*, Dohmen, Thomas, *et al.,* "Individual risk attitudes: Measurement, determinants, and behavioral consequences." Journal of the European Economic Association, Vol. 9, No. 3, June 2011, pp. 522–550; Halek, Martin, and Joseph G. Eisenhauer, "Demography of Risk Aversion" *The Journal of Risk and Insurance,* Vol. 68, No. 1, March 2001, pp. 1–24.

incremental cancer risk and will never experience any negative consequences from having consumed affected valsartan. Furthermore, the FDA recognizes the significant therapeutic benefit of valsartan and explicitly advised patients to not discontinue taking affected valsartan until speaking with their physician,[256] and the FDA states specifically that "the risks of stopping taking [sic] an ARB product for treating high blood pressure and heart failure greatly outweighs [sic] the potential risk of exposure to trace amounts of nitrosamines."[257] Clearly, based on the FDA's own assessment, the alleged risks from NDMA and NDEA exposure were not so substantial as to render the affected valsartan worthless for all patients and TPPs as Dr. Conti asserts.

139. It is also worth noting that the ex-ante and ex-post values of therapies may continually change for reasons irrespective of the potential presence of NDMA and NDEA in affected valsartan. While the choice to initiate treatment is typically based on an expectation of a drug's value, it is not uncommon for patient's response to therapy to deviate from expectation (for better or for worse). If a patient's blood pressure is not well controlled with valsartan or if side effects are not easily tolerated, a treating physician may decide to add another medication to the patient's regimen or switch the patient to an alternative medication and discontinue valsartan entirely. In both cases, and all else equal, the ex-post value would be lower than the ex-ante (expected) value. However, current reimbursement arrangements typically do not include compensation for patients or TPPs when a patient does not receive the full anticipated therapeutic benefit (nor are patients and TPPs typically asked to pay more if a therapy ultimately provides greater value than expected).

140. Overall, Dr. Conti's approach does not consider and provides no assessment of the value patients and TPPs received from affected valsartan. Dr. Conti's claim that affected valsartan

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[256] *U.S. Food & Drug Administration*, "FDA announces voluntary recall of several medicines containing valsartan following detection of an impurity," July 13, 2018, available at https://www.fda.gov/news-events/press-announcements/fda-announces-voluntary-recall-several-medicines-containing-valsartan-following-detection-impurity. *See also*, *U.S. Food & Drug Administration*, "Recalls of Angiotensin II Receptor Blockers (ARBs) including Valsartan, Losartan and Irbesartan," February 3, 2021, available at https://www.fda.gov/drugs/drug-safety-and-availability/recalls-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and-irbesartan.

[257] *U.S. Food & Drug Administration*, "Statement of the Agency's Ongoing Efforts to Resolve Safety Issue with ARB Medications," August 28, 2019, available at: https://www.fda.gov/news-events/press-announcements/statement-agencys-ongoing-efforts-resolve-safety-issue-arb-medications.

was "worthless" to members of the proposed economic loss class is premised on a hypothetical where patients would not have received affected valsartan and where she claims that there would be no equilibrium price nor value of a product without legitimate supply. This framework fails to consider the fact that patients *in fact received* therapeutic benefits from taking the affected valsartan and fails to account for those benefits when determining the value of the affected valsartan to patient and TPP members of the proposed economic loss class. Affected valsartan was clearly not "worthless" to all patients and TPPs—from either a medical or economic perspective—as Dr. Conti claims. Many patients who were treated with affected valsartan received its therapeutic benefit for treating their hypertension and/or heart failure. Assessing whether, and to what extent, the ex-post value differs from the ex-ante value in light of potential NDMA and NDEA risks is a matter of individualized inquiry and cannot be done on a class-wide basis.

David Chan, MD, PhD

January 12, 2022

CURRICULUM VITAE

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Current Academic Positions:

11/2021 – present	Associate Professor of Health Policy (with Tenure), Stanford University
9/2021 – 11/2021	Assistant Professor of Health Policy, Stanford University
11/2019 – 9/2021	Assistant Professor of Medicine, Stanford University (Reappointment)
9/2013 – 10/2019	Assistant Professor of Medicine, Stanford University (Initial Appointment)
9/2013 – present	Investigator, Center for Health Care Evaluation, Department of Veterans Affairs Health Care System
6/2014 – present	Faculty Research Fellow, National Bureau of Economic Research
2/2016 – present	Faculty Fellow, Stanford Institute for Economic Policy Research
11/2017 – 10/2019	Assistant Professor of Health Research and Policy, Stanford University (by courtesy)

Education:

1999	BA, Mathematics and Economics, *summa cum laude*, University of California at Riverside
2002	MSc, International Health Policy, distinction, London School of Economics and Political Science
2003	MSc, Economics for Development, University of Oxford
2005	MD, Medicine, University of California at Los Angeles
2013	PhD, Economics, Massachusetts Institute of Technology

Postdoctoral Training:

6/2008-6/2011	Fellow, Harvard Medical School Faculty Development Fellowship General Internal Medicine, Brigham and Women's Hospital/Harvard Medical School
6/2006-6/2008	Resident, Internal Medicine, Brigham and Women's Hospital
6/2005-6/2006	Intern, Internal Medicine, Brigham and Women's Hospital

Past Academic Appointments:

11/2010 – 6/2013	Instructor in Medicine (BIDMC), Harvard Medical School

Appointments at Hospitals/Affiliated Institutions:

8/2013 – present	Staff Physician, Internal Medicine, Palo Alto Veterans Affairs Health Care System
11/2010 – 6/2013	Staff Physician, Medicine/General Medicine, Beth Israel Deaconess Medical Center
12/2008 – 6/2013	Staff Physician, Medicine/Internal Medicine, McLean Hospital, Massachusetts General Physicians Organization
7/2008 – 6/2013	Staff Physician, Medicine/Internal Medicine, Brigham and Women's Hospital

Other Professional Positions:

2011 – 2012	Entrepreneur in Residence, White House Office of Science and Technology Policy and US Food and Drug Administration
2008 – 2010	Staff Fellow, Office of Planning and Analysis, Center for Drug Evaluation and Research, US Food and Drug Administration
2007 – 2008	Medical Device Fellow, Center for Devices and Radiological Health, US Food and Drug Administration
2019 – present	Advisory Committee Member, NBER Roybal Center for Behavioral Change in Health

Working Papers

1. Selection with Skills: Evidence from Radiologists. 2021 May, NBER Working Paper 26467, available at https://www.nber.org/papers/w26467. Accepted at *Quarterly Journal of Economics*. (with Matthew Gentzkow and Chuan Yu)

2. Fixing Misallocation with Guidelines: Awareness vs. Adherence. 2021 July, NBER Working Paper 27467, available at https://www.nber.org/papers/w27467. (with Jason Abaluck, Leila Agha, Daniel Singer, and Diana Zhu)

3. A Doctor Will See You Now: Physician-patient Relationships and Clinical Decisions. 2016 September, NBER Working Paper 22666, available at https://www.nber.org/papers/w22666. (with Marit Rehavi, Erin Johnson, and Daniela Carusi)

Publications (Economics):

1. Influence and Information in Team Decisions: Evidence from Medical Residency. *American Economic Journal: Economic Policy* 2021 Feb; 13(1): 106-37.

2. Provider Discretion and Variation in Resource Allocation: The Case of Triage Decisions. *American Economic Association Papers and Proceedings* 2020 May; 110: 279-283. (with Jonathan Gruber)

3. Industry Input in Policymaking: Evidence from Medicare. *Quarterly Journal of Economics* 2019 August; 134(3): 1299-1342. (with Michael Dickstein)

4. The Efficiency of Slacking Off: Evidence from the Emergency Department. *Econometrica* 2018 May; 86(3): 997-1030.

5. Teamwork and Moral Hazard: Evidence from the Emergency Department. *Journal of Political Economy* 2016 June; 124(3): 734-770.

6. How Sensitive Are Low Income Families to Health Plan Prices? *American Economic Association Papers and Proceedings* 2010 May; 100(2): 292-6. (with Jonathan Gruber)

Publications (Health Policy and Health Services Research):

1. Reif, Julian, **David C. Chan**, Damon Jones, Laura Payne, David Molitor. Effects of a Workplace Wellness Program on Employee Health, Health Beliefs, and Medical Use: A Randomized Clinical Trial. *JAMA Internal Medicine* 2020 May 26. Doi:10.1001/jamainternmed.2020.1321. [Epub ahead of print].

2. **Chan**, **David C.,** Johnny Huynh, David M. Studdert. The Accuracy of Valuations of Surgical Procedures in the Medicare Fee Schedule. *New England Journal of Medicine* 2019 Apr 18; 380(16):1546-1544.

3. Joynt, Karen E., **David C. Chan**, Jie Zheng, John E. Orav, Ashish K. Jha. The Impact of Massachusetts Health Care Reform on Access, Quality, and Costs of Care for the Already-Insured. *Health Services Research* 2014 Sep 15. doi: 10.1111/1475-6773.12228. [Epub ahead of print].

4. Joynt, Karen E., **David C. Chan**, John E. Orav, Ashish K. Jha. The Impact of Massachusetts Healthcare Reform on Preventable Hospitalizations for Previously Insured Medicare Patients. *Health Affairs* 2013 Mar; 32(3):571-578.

5. **Chan, David C.**, William H. Shrank, David Cutler, Michael A. Fischer, M. Alan Brookhart, Jerry Avorn, Daniel Solomon, Niteesh K. Choudhry. Patient, Physician, and Payment Predictors of Statin Adherence. *Medical Care* 2010 Mar; 48(3):196-202.

6. Jha, Ashish K., **David C. Chan**, Abigail Ridgway, Cal Franz, David W. Bates. Improving Safety and Eliminating Redundant tests: Cutting Costs in US hospitals. *Health Affairs* 2009; 28(5):1475-1484.

7. **Chan, David C.**, Philip K. Pollett, Milton C. Weinstein. Quantitative Risk Stratification in Markov Chains with Limiting Conditional Distributions. *Medical Decision Making* 2009; 29:532-540.

8. **Chan, David C.**, Paul A. Heidenreich, Milton C. Weinstein, Gregg C. Fonarow. Heart Failure Disease Management Programs: A Cost-Effectiveness Analysis. *American Heart Journal* 2008; 155(2):332-338.

Policy Briefs

1. Soldiering On: Improving Policies to Benefit America's Veterans. 2021 February. Stanford Institute for Economic Policy Research Policy Brief. (with Mark Duggan and Audrey Guo)

Work in Progress

1. Is There a VA Advantage? Evidence from Dually Eligible Veterans. (with David Card and Lowell Taylor)

2. Triage Judgments in the Emergency Department. (with Jonathan Gruber, Peter Hull, and Chris Walters)

3. Regulating by Quantity in Medicare. (with Maria Polyakova)

Honors and Prizes:

2021	*American Economic Journal: Economic Policy* Excellence in Refereeing Award
2019	Stanford Department of Medicine Teaching Award
2014	NIH Director's Early Independence Award
2011	George and Obie Schultz Fund Award, MIT Department of Economics
2007	Martin P. Solomon Education Grant, Brigham and Women's Hospital
2006	Neil R. Powe Award for epidemiology and outcomes research, Johns Hopkins University School of Medicine
2005	William N. Valentine Award for highest scholarly distinction in Internal Medicine, UCLA David Geffen School of Medicine
2002-2003	George Webb Medley Grant, Oxford University, England
2002	Brian Abel-Smith for best dissertation, London School of Economics
2001-2003	British Marshall Scholarship, Association of Commonwealth Universities
2001	Rhodes Scholarship National Finalist, The Rhodes Trust
1998	Phi Beta Kappa (early election in Junior year), Phi Beta Kappa Honor Society
1997-1999	Chancellor's List, University of California at Riverside

1997	Omicron Delta Kappa, Omicron Delta Kappa Honor Society
1997	Golden Key, Golden Key Honor Society
1995-1999	Dean's List, University of California at Riverside
1995-1999	National Merit Scholarship, National Merit Scholarship Corporation
1995-1999	Regents Scholarship, University of California at Riverside
1999	Mark P. Hanna Award for best graduating mathematics major, University of California at Riverside

Funding Information:

Current:

2018-2022	*Evaluating the VA Make-or-Buy Decision in Emergency Care* VA HSRD 1 I01 HX002631-01, PI, $1,093,544

Past:

2016-2020	*The Impact of Local Coverage Determinations on Costs and Patient Outcomes* NIH P30AG012810 (Pilot), Pilot Project Leader (Wise PI), $33,000
2014-2020	*The Benefit and Burden of Electronic Reminders in Optimizing Patient Care* NIH DP5OD019903-01, PI, $1,250,000
2016-2017	*Evaluating Preferences and Training Outcomes from the Residency Match* NIH AG017253 (Pilot), Pilot Project Leader (Bhattacharya PI), $25,000
2015-2017	*Physician Behavior and Organizational Productivity* NIH Loan Repayment Program NIH 1 L30 AG051189-01, PI, $70,000
2014-2015	*The Role of the Doctor-patient Relationship in Decision-making* P30AG024957-10 Seed, Co-PI (Chan and Chee PIs), $14,639
2013-2014	*Causes and Consequences of Physician Practice Patterns: Evidence from VA Primary Care* VA HSR&D LIP 14-CC1, Co-PI (Chan and Chee PIs), $17,317
2011-2014	*Estimating the Potential Medicare Savings from Comparative Effectiveness Research* NIH R37-150127-5054662-0002, Investigator (Garber PI)

2011-2013	*The Effect of Universal Health Care on the Previously Insured: Evidence from Medicare in Massachusetts* Rx Foundation, Co-PI (Jha PI), $254,028
2011-2013	*Social Networks and Peer Effects Among Emergency Physicians* Charles A. King Trust Postdoctoral Fellowship, PI, $95,000
2011-2013	*Peer Effects in the Emergency Department on Productivity and Patient Choice* AHRQ F32-HS021044, PI, $123,008
2011	National Bureau of Economic Research Fellowship in Aging and Health Economics NIA/T32 AG000186 Declined due to other funding

Invited Presentations (since 2013, including Scheduled):

1. University of Chicago Harris School of Public Policy; Chicago, IL (11/3/2021)
2. UCLA, Anderson School of Management; Los Angeles, CA (10/29/2021)
3. University of Chicago, Stigler Center; Chicago, IL (10/21/2021)
4. Harvard Medical School, Department of Health Care Policy; Boston, MA (9/24/2021)
5. Northwestern University, Kellogg School of Management; Evanston, IL (9/22/2021)
6. Imperial College London, Economics; London, UK (virtual) (5/4/2021)
7. Boston University / Harvard / MIT Health Economics Seminar; Boston, MA (virtual) (4/28/2021)
8. University of Bristol, Economics; Bristol, UK (virtual) (4/21/2021)
9. NBER Health Care; virtual, national attendance (12/3/2020)
10. Wharton Operations, Information, and Decisions (OID); Philadelphia, PA (virtual) (10/19/2020)
11. Western Economic Association International; Denver, CO (6/26/2020, cancelled due to COVID-19)
12. American Thoracic Society, Keynote Address; Philadelphia, PA (5/16/2020, cancelled due to COVID-19)
13. Brigham Young University, Economics; Provo, UT (4/16/2020, cancelled due to COVID-19)
14. Whistler Junior Health Economics Summit; Vancouver, Canada (3/6/2020)
15. American Economic Association Annual Meeting; San Diego, CA (1/4/2020)
16. Analysis Group; Boston, MA (12/17/2019)
17. Northwestern University, Economics and Kellogg School of Management; Evanston, IL (12/12/2019)
18. McGill University, Economics; Montreal, Canada (11/16/2019)
19. Rice University, Baker Institute of Policy Roundtable; Houston, TX (11/8/2019)
20. Erasmus University, Economics; Rotterdam, Netherlands (10/25/2019)
21. University College London, Economics; London, UK (10/28/2019)

22. Department of Veterans Affairs; Washington, DC (9/23/2019)
23. Lund University, Economics; Lund, Sweden (9/12/2019)
24. University of Copenhagen, Economics; Copenhagen, Denmark (9/11/2019)
25. NBER Summer Institute Health Care; Cambridge, MA (7/25/2019)
26. American Society of Health Economists Conference; Washington, DC (6/24/2019)
27. NBER Machine Learning in Health Care; Cambridge, MA (5/9/2019)
28. University of Chicago, Health Economics Annual Conference; Chicago, IL (4/27/2019)
29. UC Berkeley Labor; Berkeley, CA (4/11/2019)
30. Carnegie Mellon University Tepper School of Business; Pittsburgh, CA (3/5/2019)
31. National University of Singapore; Singapore (12/6/2018)
32. National Taiwan University; Taipei, Taiwan (12/4/2018)
33. Hong Kong University Business and Economics; Hong Kong (12/3/2018)
34. Princeton University, Economics; Princeton, NJ (11/19/2018)
35. RAND, Applied Microeconomics; Santa Monica, CA (11/5/2018)
36. UC Santa Barbara, Economics; Santa Barbara, CA (10/17/2018)
37. McGill University, Economics; Montreal, Canada (10/3/2018)
38. HEC Montreal, Economics; Montreal, Canada (10/2/2018)
39. New York City Health Economics Seminar (Columbia, Cornell, CUNY, NYU); New York, NY (9/6/2018)
40. Columbia University Department of Economics; New York, NY (9/4/2018)
41. NBER Summer Institute Health Care; Cambridge, MA (7/27/2018)
42. Society for Institutional and Organizational Economics; Montreal, Canada (6/23/2018)
43. American Society of Health Economists Biennial Conference; Atlanta, GA (6/11/2018)
44. NBER Machine Learning in Health Care; Cambridge, MA (6/4/2018)
45. London School of Economics; London, UK (5/15/2018)
46. UC Berkeley Industrial Organization; Berkeley, CA (5/8/2018)
47. Duke Law School; Durham, NC (4/6/2018)
48. UC San Diego Economics; San Diego, CA (4/2/2018)
49. University College Dublin; Dublin, Ireland (3/16/2018)
50. Chicago Booth Junior Health Economics; Vancouver, Canada (2/16/2018)
51. Harvard / MIT / Stanford / World Bank Empirical Management Conference; Washington, DC (12/7/2017)
52. George Washington University; Washington, DC (12/6/2017)
53. NBER Organizational Economics; Cambridge, MA (11/18/2017)
54. University of Pennsylvania Leonard Davis Institute; Philadelphia, PA (11/10/2017)
55. Cornell Economics and Policy (joint); Ithaca, NY (11/8/2017)
56. Annual Health Economics Conference (AHEC); Los Angeles, CA (10/20/2017)
57. MIT Organizational Economics; Cambridge, MA (10/12/2017)
58. Harvard Medical School Department of Health Care Policy; Boston, MA (10/11/2017)
59. Caltech; Pasadena, CA (10/3/2017)
60. USC Schaeffer Health Policy Center; Los Angeles, CA (9/12/2017)
61. International Health Economics Association World Congress; Boston, MA (7/10/2017)

62. Society for Institutional and Organizational Economics SIOE) Annual Meeting; New York, NY (6/19/2017)
63. Highland Health Economics Symposium; Roshven, Scotland, UK (6/19/2017)
64. Washington University Olin Business School); St. Louis, MO (5/12/2017)
65. US Federal Trade Commission; Washington, DC (4/24/2017)
66. US Department of Justice; Washington, DC (4/23/2017)
67. University of Illinois; Champaign, IL (4/11/2017)
68. Montreal Political Economy Conference; Montreal, Canada (3/30/2017)
69. Simon Fraser University; Burnaby, Canada (3/8/2017)
70. University of British Columbia; Vancouver, Canada (3/7/2017)
71. Berkeley-Stanford Health Economics Workshop; Stanford, CA (2/24/2017)
72. Chicago Booth Junior Health Economics; Vancouver, Canada (2/17/2017)
73. American Economic Association Annual Meeting; Chicago, IL (1/6/2017)
74. Western Economic Association International; Portland, OR (7/1/2016)
75. American Society of Health Economists Biennial Conference; Philadelphia, PA (6/14/2016)
76. Universat Pompeau Fabra; Barcelona, Spain (4/14/2016)
77. University of Munich; Munich, Germany (4/12/2016)
78. University College London; London, UK (4/11/2016)
79. NBER Health Care; Cambridge, MA (3/11/2016)
80. Boston University / Harvard / MIT Health Economics Seminar; Boston, MA (3/9/2016)
81. UT Austin Economics; Austin, TX (2/29/2016)
82. Tulane; New Orleans, LA (2/19/2016)
83. Johns Hopkins Carey Business School; Baltimore, MD (12/9/2015)
84. University of North Carolina Economics; Chapel Hill, NC (11/3/2015)
85. Duke Fuqua Business School; Durham, NC (11/2/2015)
86. Chicago Booth Applied Economics; Chicago, IL (10/28/2015)
87. US Department of Justice; Washington, DC (10/21/2015)
88. University of Maryland Economics; College Park, MD (10/20/2015)
89. University of Rochester; Rochester, NY (10/16/2015)
90. Paris School of Economics; Paris, France (9/30/2015)
91. Toulouse School of Economics; Toulouse, France (9/28/2015)
92. University of Arizona Economics; Tucson, AZ (9/3/2015)
93. Western Economic Association International; Honolulu, HI (6/30/2015)
94. Queen's University Economics of Organization; Kingston, Canada (6/11/2015)
95. University of Toronto Rotman and Economics); Toronto, Canada (6/9/2015)
96. USC Schaeffer Health Policy Center; Los Angeles, CA (6/3/2015)
97. UC Irvine Economics and Business School; Irvine, CA (6/2/2015)
98. New York City Health Economics Seminar (Columbia, Cornell, CUNY, NYU); New York, NY (5/15/2015)
99. Cornell Weill Medical College; New York, NY (5/14/2015)
100. NBER Organizational Economics; Cambridge, MA (4/24/2015)
101. Rice University Economics; Houston, TX (4/21/2015)
102. Columbia Business School; New York, NY (4/8/2015)
103. NBER Productivity Innovation and Entrepreneurship; Cambridge, MA (3/20/2015)
104. Chicago Booth Junior Health Economics; Vancouver, Canada (3/14/2015)

105. Carnegie Mellon University Heinz College; Pittsburgh, PA (2/27/2015)
106. Case Western Reserve University Economics; Cleveland, OH (2/18/2015)
107. American Economic Association Annual Meeting; Boston, MA (1/3/2015)
108. Veterans Affairs Center for Health Care Evaluation; Menlo Park, CA (9/30/2014)
109. RAND; Santa Monica, CA (9/22/2014)
110. NBER Summer Institute Personnel Economics; Cambridge, MA (7/24/2014)
111. International Health Economics Association World Congress; Dublin, Ireland (7/16/2014)
112. American Society of Health Economists Biennial Conference; Los Angeles, CA (6/24/2014)
113. Cornell Law School; Ithaca, NY (4/11/2014)
114. MIT Organizational Economics; Cambridge, MA (4/10/2014)
115. ETH Zurich; Zurich, Switzerland (2/19/2014)
116. Queen's School of Business; Kingston, Canada (2/7/2014)
117. American Economic Association Annual Meeting; Philadelphia, PA (1/4/2014)
118. NBER Summer Institute Health Care (7/25/2013)
119. Dartmouth College; Hanover, NH (3/13/2013)
120. USC Price School of Public Policy; Los Angeles, CA (3/6/2013)
121. Johns Hopkins Carey Business School; Baltimore, MD (2/15/2013)
122. Johns Hopkins Bloomberg School of Public Health; Baltimore, MD (2/14/2013)
123. Columbia School of Public Health; New York, NY (2/8/2013)
124. Duke Fuqua Business School; Durham, NC (2/6/2013)
125. Carnegie Mellon University Heinz College; Pittsburgh, PA (2/4/2013)
126. Cornell Weill Medical College; New York, NY (2/1/2013)
127. Yale Public Health; New Haven, CT (1/30/2013)
128. Harvard Business School; Cambridge, MA (1/28/2013)
129. University of Pennsylvania Medical School; Philadelphia, PA (1/22/2013)
130. University of Michigan Ross School of Business; Ann Arbor, MI (1/22/2013)
131. University of Michigan Medical School; Ann Arbor, MI (1/22/2013)
132. USC Schaeffer Health Policy Center; Los Angeles, CA (1/18/2013)
133. Harvard Medical School Department of Health Care Policy; Boston, MA (1/15/2013)
134. University of Pennsylvania Wharton School of Business; Philadelphia, PA (1/14/2013)
135. UCLA David Geffen School of Medicine; Los Angeles, CA (1/8/2013)
136. RAND; Santa Monica, CA (1/7/2013)

Current Licensure and Certification:

2007-	Medical License, Commonwealth of Massachusetts
2008-2019	Diplomate, American Board of Internal Medicine

Professional Service

Referee: *American Economic Journal: Applied Economics*, *American Economic Journal: Economic Policy*, *American Economic Journal: Microeconomics*, *American Economic Review, American Journal of Health Economics, European Journal of Health Economics,*

JAMA Internal Medicine, *Journal of the American Medical Association, Journal of the European Economic Association*, *Journal of Health Economics, Journal of Human Resources, Journal of Labor Economics, Journal of Political Economy, Journal of Public Economics, PLOS ONE, RAND Journal of Economics*, *Quarterly Journal of Economics, Review of Economic Studies*, *Review of Economics and Statistics*, *Science*

Professional Service

Grant Proposal Reviewer:

Military Health System Research
Israel Science Foundation
US-Israel Binational Science Foundation

Journal Ad Hoc Referee:

American Economic Journal: Applied Economics
American Economic Journal: Economic Policy
American Economic Review
American Journal of Health Economics
American Journal of Managed Care
Economic Inquiry
European Journal of Health Economics
JAMA Internal Medicine
Journal of the American Medical Association
Journal of the European Economic Association
Journal of Health Economics
Journal of Human Resources
Journal of Labor Economics
Journal of Political Economy
Journal of Public Economics
Management Science
PLOS ONE
Quarterly Journal of Economics
RAND Journal of Economics
Review of Economics and Statistics
Review of Economic Studies
Science

Teaching

1. Stanford ECON/HRP/MED 249: Instructor, Topics in Health Economics (with Neale Mahoney and Maria Polyakova), 2016-

2. Stanford HRP 201: Guest Lecturer, Health Policy Graduate Student Tutorial, 2020-

3. Stanford HRP 252: Instructor, Outcomes Analysis (with Eran Ben David and Jay Bhattacharya), 2016-2019

4. Stanford: Instructor, First-year PhD Tutorial in Health Economics, 2015

5. National Bureau of Economic Research: Lecturer, Health Care Bootcamp, December 2019

APPENDIX B
PRIOR TESTIMONY IN THE LAST 4 YEARS

The People of the State of California v. Purdue Pharma et al., Case No. 30-2014-00725287-CU-BT-CXC, Deposition, February, 15, 2021.

The State of New Hampshire v. Johnson & Johnson et al., Case No. 217-2018-CV-00678, Deposition, May 27, 2021.

County of Dallas v. Purdue Pharma L.P. et al., Cause No. 2018-77098, Deposition, September 9, 2021.

APPENDIX C
MATERIALS RELIED UPON

Court Documents

Consolidated Third Amended Medical Monitoring Class Action Complaint, *Valsartan Products Liability Litigation*, November 1, 2021.

Memorandum of Law in Support of the Medical Monitoring Plaintiffs' Motion for Class Certification, *Valsartan, Losartan, and Irbesartan Products Liability Litigation*, November 10, 2021.

Third Amended Consolidated Economic Loss Class Action Complaint, *Valsartan, Losartan, and Irbesartan Products Liability Litigation*, November 1, 2021.

Expert Reports

Expert Declaration of Rena Conti, Ph. D., *Valsartan, Losartan, and Irbesartan Products Liability Litigation*, November 10, 2021.

Expert Report of Edward H. Kaplan, M.D., *Valsartan, Losartan, and Irbesartan Products Liability Litigation*, November 10, 2021.

Expert Report of Zirui Song, M.D., Ph. D., *Valsartan Products Liability Litigation*, November 10, 2021.

Rule 26 Expert Report of Dipak Panigrahy, MD, *Valsartan, Losartan, and Irbesartan Products Liability Litigation,* July 6, 2021.

Depositions and Declarations

Deposition of John Judson, February 8, 2021.

Deposition of Michael Rives, May 26, 2021.

Deposition of Paulette Silberman, March 22, 2021.

Deposition of Robert Kruk, May 12, 2021.

Deposition of Roger Tasker, May 6, 2021.

Deposition of Sarah Zehr-Johnson, May 20, 2021.

Deposition of Valerie Rodich-Annese, March 9, 2021.

Data

Centers for Medicare and Medicaid Services, "Medicare Physician & Other Practitioners - by Provider and Service," available at https://data.cms.gov/provider-summary-by-type-of-service/medicare-physician-other-practitioners/medicare-physician-other-practitioners-by-provider-and-service.

Medical Expenditure Panel Survey data

Medical Expenditure Panel Survey, Household Full Year Medical Conditions File, available at: https://meps.ahrq.gov/data_stats/download_data_files_results.jsp?cboDataYear=All&cboDataTypeY=1%2CHousehold+Full+Year+File&buttonYearandDataType=Search&cboPufNumber=All&SearchTitle=Medical+Conditions.

Medical Expenditure Panel Survey, Household Full Year Population Characteristics File, available at https://meps.ahrq.gov/data_stats/download_data_files_results.jsp?cboDataYear=All&cboDataTypeY=1%2CHousehold+Full+Year+File&buttonYearandDataType=Search&cboPufNumber=All&SearchTitle=Population+Characteristics.

Medical Expenditure Panel Survey, Household Prescribed Medicines Event File, available at https://meps.ahrq.gov/data_stats/download_data_files_results.jsp?cboDataYear=All&cboDataTypeY=2%2CHousehold+Event+File&buttonYearandDataType=Search&cboPufNumber=All&SearchTitle=Prescribed+Medicines.

Medical Expenditure Panel Survey, Longitudinal Data Codebook, available at https://meps.ahrq.gov/mepsweb/data_stats/download_data_files_codebook.jsp?PUFId=H209&varName=ADCLNS42.

MGH CMS-Required Hospital Charge Data (only includes commercial insurers), available at https://www.massgeneral.org/notices/billing/CMS-required-hospital-charge-data.

OptumHealth Care Solutions, Inc. ("*OptumHealth*") database.

Books and Articles

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